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The Effects of Reserpine and Chlorpromazine on Gastric Secretion. By BERNARD J. HAVERBACK, M.D., THOMAS D. STEVENSON, M.D., ALBERT SJOERDSMA, PH.D., M.D., and LUTHER L. TERRY, M.D. 601

The Interacting Effects of Public Health, Fertility Behavior and General Economy on Standards of Living. III. Quantitative Evaluation of Component Determinants with Respect to Raising or Maintaining Present Standards. By ALEXANDER LANGER, M.D., and PAUL S. HENSHAW, PH.D. 605

The Rectal Absorption of Mercaptomerin Labeled with HG^{203}. By JERRY K. AIKAWA, M.D., and WILLIAM R. CARLSON, M.D. 622

The Relationship of Cirrhosis of the Liver to Hypertension: A Study of 504 Cases of Cirrhosis of the Liver. By HUBERT F. LOYKE, M.D. 627

A Simple Micromethod for Determination of Bilirubin in Plasma. By JAMES H. GRAHAM, M.D. 633

The Effect of Sitosterol Administration upon the Serum Cholesterol Level and Lipoprotein Pattern. By CLAUDE JOYNER, JR., M.D., and PETER T. KUO, M.D. 636

Simultaneous Determination of Cardiovascular-Renal Functions in Man by a Constant Infusion Technique. By CHARLES H. HENDRICKS, M.D., EDWARD J. QUILLIGAN, M.D., LEO A. SAPIRSTEIN, PH.D., M.D., ANDREW J. PULTZ, A.B., M.S., and MORRIS J. MANDEL, A.B., M.S. 648

Local Cutaneous Response of Nicotinic Acid and Esters as Diagnostic Aid for Rheumatoid Arthritis. By PAUL LEIFER, M.D., and ROBERT C. BATTERMAN, M.D. 657

The Clinical Use of Erythromycin. By SAUL SOLOMON, M.D., and BARBARA JOHNSTON, M.D. 660

Progress of Medical Science

Pediatrics—A Review of Porphyrin Metabolism with Special Reference to Childhood. By ROBERT A. ALDRICH, M.D., ROBERT F. LABBE, PH.D., and ELLEN L. TALMAN, PH.D. 675

Gynecology and Obstetrics—A Five-Year Survey of the Literature in Cancer of the Cervix. By JOHN A. WALL, M.D., F.A.C.S. 698

Book Reviews and Notices 714

Complete contents on adv. page 8

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Female	114.7	116.4	117.7	118.7	120.4	123.6	127.1	129.8	132.5	133.7	135.4
DIASTOLIC **Male	76.4	78.1	78.8	79.5	80.4	81.4	82.3	83.3	84.3	84.5	84.0
Female	75.8	77.1	78.0	78.6	79.9	81.9	83.9	85.4	86.8	86.8	84.4

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*Blood Pressure, Report of Joint Committee on Mortality of The Association of Life Insurance Medical Directors and The Actuarial Society of America, New York, 1925, pp. 10, 52.

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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

DECEMBER, 1955

ORIGINAL ARTICLES

THE EFFECTS OF RESERPINE AND CHLORPROMAZINE ON GASTRIC SECRETION

By Bernard J. Haverback, M.D.

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Reserpine and chlorpromazine are being widely used in a number of clinical conditions. Reserpine is a moderately potent antihypertensive drug and chlorpromazine is useful in combating nausea and vomiting of varied etiology. Both drugs produce tranquility in neuropsychiatric disorders. The occurrence of abdominal cramps and diarrhea during reserpine administration and of constipation following the administration of chlorpromazine suggested that these drugs have an effect on the gastrointestinal tract. The studies in this report were done to evaluate the effect of reserpine and chlorpromazine on gastric secretion in man.

Procedure. RESERPINE GROUP. Thirteen studies were done on 12 patients whose ages ranged from 19 to 58 years. Except for one case of chronic duodenal ulcer, there was no evidence of gastrointestinal disease in these individuals. Following a 12-hour fast a stomach tube was positioned in the gastric antrum under fluoroscopic guidance. The fasting contents were evacuated and the gastric secretion aspirated continuously for 3 hours and 15 minutes by means of a mechanical suction pump. The volume of successive 15-minute specimens was measured, and the free acidity titrated with sodium hydroxide using Töpfer's indicator. The drug was administered intravenously in five instances and orally in eight.

In the intravenous group at the end of the third 15-minute period, an infusion of 500 cc. of 5% glucose in water was given as a control study. In the drug study 1 to 2 mg. of reserpine was added to the infusion. The total period of infusion was 30 minutes.

When reserpine was given orally, a gastric study was performed prior to the administration of the drug and then repeated 4 to 7 days after the drug was started. The dosage of reserpine was 1 to 1.5 mg. twice daily and the last dose was given 3 hours prior to the gastric study.

Each patient in both groups had a control and drug study.

CHLORPROMAZINE GROUP. Seven studies were performed on 7 patients whose ages ranged from 26 to 58 years. The subjects had no evidence of gastrointestinal disease except one who had a healed duodenal ulcer. The

gastric aspiration procedure was as previously described except that the period of study was 2 hours and 45 minutes. At the end of the third 15-minute period, 50 mg. of chlorpromazine or a saline placebo was given intramuscularly. Each patient had both a control and drug study.

Results. As shown in Fig. 1, a marked increase in both volume and free acidity occurred within 60 minutes following the intravenous administration of reserpine and persisted throughout the period of study. The average values of volume and free acidity for the last seven 15-minute periods were 12.1 cc. and 22.4 units in the control studies and 36.4 cc. and 73.8 units in the reserpine studies.

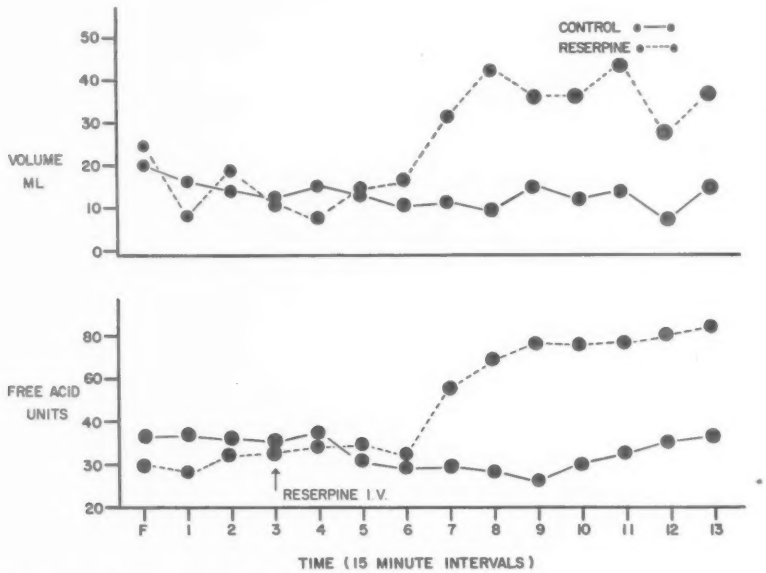

Fig. 1.—The graphs represent the average values of volume and free acidity of gastric secretion following the intravenous administration of reserpine in 5 subjects.

The results of the oral administration of reserpine are shown in Fig. 2. An increase in volume and free acidity occurred in 7 of the 8 studies but was less striking than the change produced by the intravenous administration of reserpine. The average values of volume and free acidity for the 3-hour-and-15-minute period were 14.1 cc. and 21.6 units in the control studies and 24.1 cc. and 39.0 units in the reserpine studies.

The results following the intramuscular administration of chlorpromazine are shown in Fig. 3. There was a decrease in the volume of gastric secretion without a significant change in the free acidity. The average values of volume and free acidity during the last five 15-minute periods were 22.6 cc. and 27.2 units in the control studies and 4.1 cc. and 27.8 units in the chlorpromazine studies.

Discussion. Plummer *et al.* have shown that reserpine increases the volume and acidity of gastric secretion in dogs, both in the vagally innervated gastric fistula pouch and in the vagally denervated Heidenhain pouch. They have presented data which suggest that reserpine evokes gastric secretion by stimulating the parasympathetic

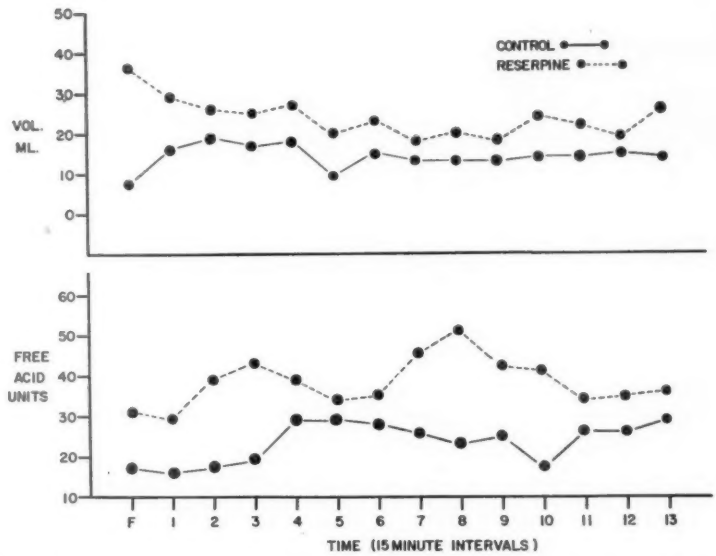

Fig. 2.—The graphs represent the average values of volume and free acidity of gastric secretion following the oral administration of reserpine in 8 subjects.

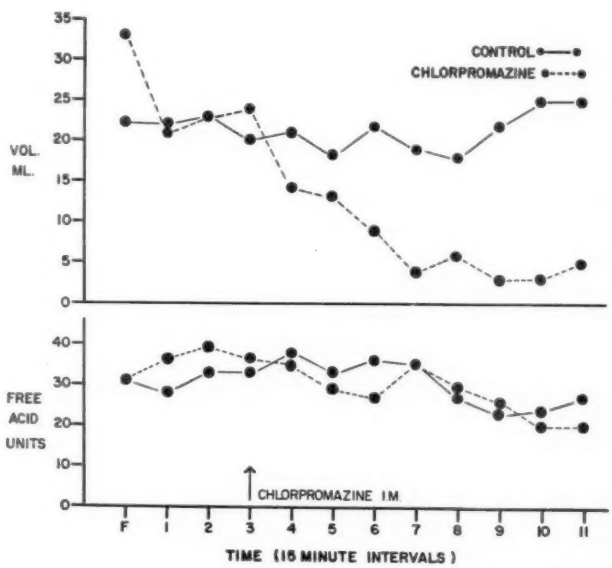

Fig. 3.—The graphs represent the average values of volume and free acidity of gastric secretion following the intramuscular administration of chlorpromazine in 7 subjects.

ganglia[1,6]. The present studies indicate that reserpine increases the volume and acidity of gastric secretion in man. In addition to the gastric secretory effects, there is evidence that reserpine stimulates the motor function of the gastrointestinal tract in animals. The abdominal cramps and diarrhea observed following the clinical use of the drug is further evidence of this effect[2,3,5].

Because of the effects on gastric secretion, reserpine should be given cautiously to patients with a peptic ulcer. We have observed gastrointestinal bleeding manifested by melena associated with severe abdominal cramps in a 42-year-old hypertensive patient while on reserpine. The patient did not have these symptoms prior to reserpine administration, and following cessation of the drug the abdominal cramps and bleeding promptly subsided. An investigation of the gastrointestinal tract showed no obvious cause of bleeding. Whether or not the administration of reserpine was coincidental with the episode of bleeding in this patient cannot be established. Hollister *et al.* reported that 2 patients with a history of duodenal ulcer had a reactivation of their symptoms while under treatment with reserpine[4].

Chlorpromazine, given intramuscularly, reduced the volume of gastric secretion but did not significantly change the free acidity. These changes are similar to those following the administration of atropine. The mechanism by which chlorpromazine decreases gastric secretion is not clearly established.

Summary. 1. Reserpine administered orally and intravenously has been shown to increase the volume and free acidity of gastric secretion.

2. Chlorpromazine reduced the volume of gastric secretion but did not significantly change the free acidity.

3. Chlorpromazine would appear to be the tranquilizing agent of choice when stimulation of gastric secretion is contraindicated.

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SUMMARIO IN INTERLINGUA

Le Effectos de Reserpina e Chlorpromazina Super le Secretion Gastric

1. Es demonstrate que reserpina in administrationes oral e intravenose augmenta le volumine e le libere aciditate del secretion gastric.

2. Chlorpromazina reduce le volumine del secretion gastric sed su effecto super le libere aciditate non es significative.

3. Nos conclude que chlorpromazina es a preferer como agente tranquilisante in casos in que un stimulation del secretion gastric es contraindicate.

THE INTERACTING EFFECTS OF PUBLIC HEALTH, FERTILITY BEHAVIOR AND GENERAL ECONOMY ON STANDARDS OF LIVING. III. QUANTITATIVE EVALUATION OF COMPONENT DETERMINANTS WITH RESPECT TO RAISING OR MAINTAINING PRESENT STANDARDS

By Alexander Langer, M.D.

and

Paul S. Henshaw, Ph.D.*

Based on the idea that level of living in a country or territory varies with the availability of materials needed for life, and, at the same time, with the number of people making demands for such materials, evidence has been presented in the first two papers of this series[2,3] calling attention to birth and death rates, population increase rates, population density, and per capita caloric intake, industrial energy consumed and income, as significant elements involved in determining level of living. Further, it was pointed out that representative values for these elements can be used to obtain measures of total fertility, population pressure, economic development, and finally an over-all Situation Index useful for comparing conditions of living in different places and at different times.

Total fertility, as defined for these studies, consists of two components: one, actual fertility, which is the existent multiplying population, and, the other, "wasted" fertility, which is comprised of premature deaths largely saveable (when means are available) by methods now well known. Since fertility, both actual and wasted, is influenced and to a considerable extent determined by conditions of health resulting from public health practices, or lack of such practices, it is appropriate to look upon fertility as primarily a health feature in the over-all picture.

Population pressure, consisting also of two main elements, total fertility and population density (people per km^2), contains one fixed feature, namely, total land area. So far as population pressure is concerned, therefore, density of population varies directly with fertility, and, as just indicated, it is influenced strongly by public health measures as they affect either birth or death rates.

Economic development, as defined, consists of three main elements: per capita food intake per day, industrial energy consumed per person per year, and average annual income per person, each specified in a particular way. In a certain sense, each of these comprises a kind of summation of human advancements. Food utilization per person gives an indication of agricultural advancement, energy consumed an indication of industrialization achieved, and income per person an indication of the abilities and skills, including those used in agriculture and industry, which are employed in making a living in the region of residence. Each of these, it may be said, reflects the degree of advancement made in educational, technical and social develop-

*National Committee on Maternal Health, Inc., 2 East 103rd Street, New York 29, New York.

ment, including progress in health. A combined figure, or product, of values for caloric intake, energy consumed and income, has, therefore, been taken as representative of economic development and as a measure of level of living.

The over-all Situation Index, then, is not in itself a measure of level of living but rather an "index" of it. Economic development, as visualized here, is much more a measure of actual living conditions, although in some respects it also acts as a determinant. Accepting the central idea that level of living varies with availability of materials and with the number of people making demands for them, it follows that population pressure acts against or in opposition to economic development or level of living, and that the level of living index will be influenced by changes in economic conditions or in population pressure. Accordingly, by calculating the ratio of population pressure to economic development, we obtain index figures that are useful for purposes of comparison. More important, we have available a formula into which different values for the elements of population pressure and economic development can be inserted, thereby obtaining impressions of the character and magnitude of changes required for different amounts of improvement. Going further, we have at the same time a means of obtaining impressions of the component elements most likely to bring down level of living in countries and territories where higher levels now exist.

Based on recent statistical data (United Nations sources, see Paper 1) and utilizing the over-all Situation Index values as a guide, or as a basis from which to work, it will be our purpose here to examine the figures for conditions in countries and territories much in need of better standards of living, arbitrarily substituting higher values for the component determinants and arriving thereby at ideas as to the most practical means of obtaining significant improvements. In the light of these considerations, it will also be our purpose to examine the conditions in countries and territories that are better off, deriving impressions concerning the kinds of conditions to be guarded against.

Taking into account 70 countries and territories, Situation Index values (in logarithms) were found to vary from approximately -3 to $+3$ and to be less than logarithm 0, or 1, for 34, or almost half, of them. In a general way, then, we shall deal with those having a Situation Index less than 1 in one group and those with an Index more than 1 in another.

ANALYSIS 1. At the outset, it was natural to think in terms of lifting the level of living in less developed countries to, or at least toward, a condition yielding a Situation Index of 1 as a target, one which at present is intermediate but which nevertheless is low compared with achievements in many countries. Accordingly, it was decided to ascertain the conditions when birth, death and population increase rates are, respectively, 1.5, 1.0 and 0.5% per year; when population density remains as at present; when caloric intake is at a level visualized by the United Nations Food and Agricultural Organization (FAO) as possible by 1960[4]; when industrial energy consumed is 10% higher than at present; and when income per person is 20% higher.

Results are shown in Fig. 1. In the middle section, names of countries and territories are arranged according to existing levels on the Situation Index scale. The first projections to the right or left show changes which would result from the birth and death rate modi-

fications alone: that is, when they become 1.5 and 1.0, respectively, giving a population increase rate of 0.5 (Condition 1). The second projections, also right and left, show the additional changes resulting from modifications of caloric intake, energy consumed and income, as described (Condition 2). Projections to the left are those which show the greatest amount of change resulting from birth and death rate modifications, and those to the right show the greatest change (arithmetically) which results from industrial and socio-agricultural improvements.

Since, in this analysis, the object with respect to less developed countries was to move toward conditions characteristic of the more industrialized countries, birth rate was set at 1.5 and death rate at 1.0, in part, to give a population increase rate of 0.5, which approximates that in many countries where industrialization is advanced. A death rate of 1.0 was chosen because it is a level, as explained in Paper 1 and as mentioned above, approached when well organized public health programs are operating; also, because it is a condition capable of being achieved by the types of health development being introduced so widely throughout the world. The resulting birth rate, while to some extent characteristic of economically advanced countries, is unusually low when compared with that in most economically underdeveloped countries. This feature will be discussed in greater detail after consideration has been given to the possibilities of lifting levels of living mainly by economic improvement. With respect to caloric intake, it was a matter of practical significance to take food targets regarded by the FAO as achievable by 1960 even though in many cases the level would be less than that required for fully healthful nutrition. For industrial energy consumed per capita, an increase of 10% over existing levels was chosen arbitrarily because such an increase is sometimes achievable in periods of 5 to 10 years. Lastly, for income per capita, an increase of 20% over existing levels was also selected arbitrarily. The latter is somewhat disproportionate inasmuch as industrialization and income tend to go along together. The figure of 20% increase in income, however, will serve our purposes more suitably since, in certain of the later analyses, the figure for industrialization will be varied (mostly upward) while other conditions will be kept constant.

Looking now at Fig. 1, it is seen that even with the substantial improvements visualized, only a few of the countries in the lower range group (seven) were raised to a point on the Situation Index scale of one or above. This means that although the public health conditions may be at a theoretically favorable maximum, the conditions of population pressure and economic development are so unfavorable that the economic improvements visualized would not in most cases be sufficient to create conditions approaching the present intermediate low level. It is obvious from looking at the figure, that lifting Egypt, for example, from the present level to a point where it would have an Index value of 1 would be equivalent to lifting Mexico from the existing level to one similar to the United States. The change would be very great.

ANALYSIS 2. In order to obtain impressions of the magnitude of change in consumption of industrial energy actually required to bring the lower level countries to have a Situation Index of 1, calculations have been made and the results given in Table 1.

In the first two columns to the right of the names of the countries and territories, present Situation Index values

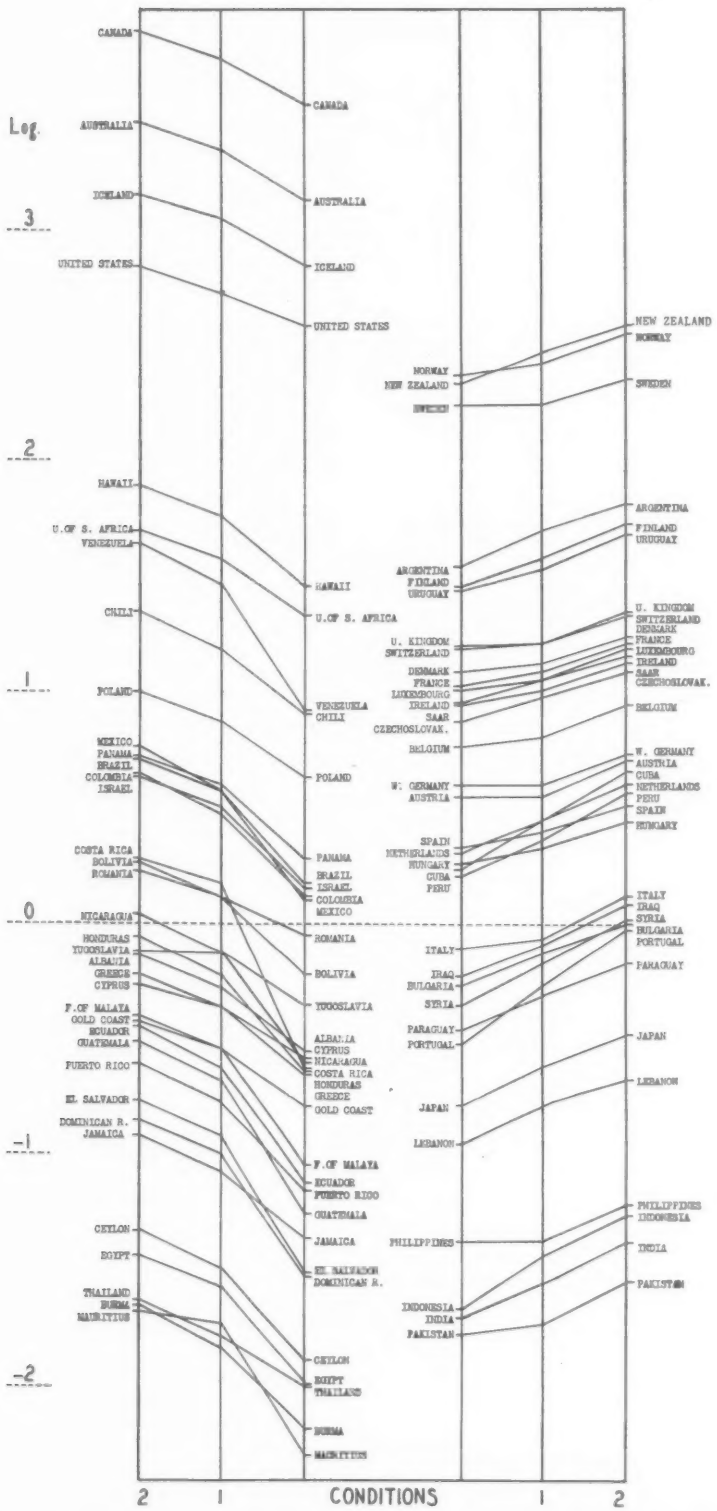

Fig. 1.—Situation Index changes resulting from arbitrarily chosen values for component determinants, Conditions 1 and 2 as defined in the text.

and present energy consumption levels per capita are shown (data from Paper 1). When the changes in energy consumption alone are used to raise the Situation Index values to 1, the amounts required are shown in the next column, the one headed "Condition A." By comparing the figures for existing levels with those for Condition A, it is seen that the increases vary from less than 10 to more than 100 times, which in terms of achievement is unrealistic when we think of 5 and 10% increases in a period of several years as being significant accomplishments.

Since other improvements usually go along with industrialization, when it occurs, other conditions were considered the same as was done in Analysis 1 above: Condition B, where birth and death rates are 1.5 and 1.0, respectively; Condition C, where caloric intake is that visualized as possible by 1960, and income is 20% higher than existing levels; and, Condition D, which combines all of these. The amount of energy consumption required for each Condition to bring the Situation Index to 1 then was calculated. The most tangible situation so far as energy increase requirements are concerned is Condition D, but even here, as may be seen, the amount of change necessitated is in most cases very large. Column X shows the magnitudes of change necessary for this condition. It will be noted that whereas some of the countries would require no increase in energy consumption (indicated by blank spaces) most of them would require a hundred to a good many hundred per cent increase.

The picture may be rendered more vivid by considering the necessary increases in terms of coal. Column Y shows present total amounts of energy consumed in tons coal equivalent in millions. Multiplying these figures by the number of times energy consumption must be increased (Column X), we obtain the values given in Column Z where total tons coal equivalent are also shown in millions. Here it is seen that the figures in a number of cases are enormous. India, for example, would need an increase in energy consumption equivalent to 950 million tons, and this in addition to the unusually favorable conditions of health and of economic developments of other types. Similarly, Japan, Pakistan, Egypt and Indonesia, would need increases of 230, 140, 130 and 77 million tons, respectively. Even allowing for improvements of the greatest magnitude, such changes, it seems safe to say, are unlikely of achievement in any short interval of time. In the case of India, such a change would be as great as quickly lifting that country to a level of energy consumption almost equal to that of the United States, which at present is 1,200 million tons coal equivalent per year. It must be concluded, therefore, that for most of the countries and territories under consideration here, a Situation Index of 1 as a goal to be achieved in the foreseeable future is unrealistic.

Before leaving this Analysis, however, it is important to understand why the conclusion just reached is true. In the Situation Index formula, as we have pointed out energy consumption per capita is an important determinant of economic development or level of living, as well as a measure of them. When this factor is exceedingly small at the outset (which is the case in countries that have primarily an agricultural economy) and when it is kept small by population pressure, resulting either from high fertility or high population density, the amount of increase must necessarily be very large. In case of India, per capita energy consumption at the present time is particularly

low; in the case of Japan, it is higher but counteracted by higher density; and in the case of Egypt, energy consumption is low and population density is high, making a double handicap. Character of the impediments to improvement differs in different localities, and this must be understood if advancements are to be accomplished by the most efficient means.

ANALYSIS 3. Before coming to what appears to be the most efficient means of improvement, let us consider one other special condition, that of increasing the Situation Index only 10-fold (a change of 1 on the logarithmic scale) for countries in the lower range group. Such a change would be more tangible of achievement than the conditions of Analysis 2 and, therefore, more realistic in most cases. While an improvement not nearly as much as might be desired, it would nevertheless be a goal or target worthy of consideration.

Results of calculations are shown in Table 2* where the arrangement is the same as that employed in Table 1. Naturally, the necessary changes are not as large. When increases are obtained by modifying energy consumption alone (Condition A), the resulting figures, while varying widely, are much more uniform than when energy is changed sufficiently to bring the Situation Index all the way to 1 as done in Analysis 2. Similarly, for Condition D, the resulting values are also more uniform. Increases in a good many instances nevertheless are high, and, if achievable at all, only with major effort. This finding makes consideration of still other conditions a matter of importance.

ANALYSIS 4. As recognized continuously throughout these discussions, birth and death rates act to determine fertility, and fertility in turn acts to affect standard of living. Most of the countries in the group under consideration thus far have both high birth rates and high death rates. Changing to birth rate 1.5 and to death rate 1.0 as visualized in the previous Analyses are major modifications and require some elucidation.

Controlling births in a manner paralleling the control of deaths, for the most part, has not been a matter of public concern heretofore, particularly in Western countries, which, until recently, have been involved with colonization and expansion of the frontier. Now that the frontier is effectively closed and that the era of expansion is giving way to an era of concentration, it is to be expected that increasing attention will be given to rates of population growth in relation to the availability of resources. Practices such as emigration, late marriage, employment of women, and others, reduce fertility or hold it in check, but not significantly in time as a rule. That birth rates can be reduced by generalized action on the part of the people is made evident by recent practices in Japan where birth management (mainly by abortion) has been widely accepted. In that country, birth rates have fallen from 3% per year to approximately 2% since 1950. Taking as a fact that there are suitable means of statistically reducing fertility (means that are simple, safe and inexpensive, and in a category quite apart from the wastage of abortion) it is not impractical to think in terms of reducing birth rates 25% in a reasonable time when there is general desire on the part of people to do so. For this analysis, therefore, 25% reduc-

*Data given in Paper I are based on slide rule calculations and, therefore, involve small errors. Full calculations have been made for this paper, thus accounting for slight discrepancies.

tion below existing levels will be considered as a target.

Reducing death rates to the range of 1.0% per year has been demonstrated widely to be tangible of achievement. Accordingly, we shall hold to a death rate of 1.0% as an objective.

Taking as a general health objective, then, 25% reduction in birth rates and death rates reduced to 1.0% per year, calculations were made. Results are indicated by the first projection from the charted existing Situation Index levels in Fig. 2 (Condition 1).

So far as food available for consumption is concerned, it is doubtful that any improvement can be made on the 1960 targets set by the FAO. The figures given by FAO are probably as near a maximum as would be capable of being achieved. We shall therefore use these values also in what will be regarded as our more practical approach.

Two levels of energy consumption will be used in this approach: first, 10% increase over existing levels as was done in Analysis 1, and, second, increases of the amount required to raise the Situation Index values 10-fold (the amounts derived in Analysis 3). The first level may be regarded as a significant increase and the second as achievable in a good many instances when significant amounts of investment capital and human motivation are available or are existent.

With respect to income, we shall hold to 20% increase over existing levels, which, as indicated above, is rather large but often achievable by more efficient management, better educational facilities, improved social organization, technical developments and higher wages.

Adding to the improvements obtained by reducing birth rates 25% and bringing death rates to 1.0% per year the further improvements of raising per capita food intake to FAO 1960 target levels, raising energy consumption 10% and raising income 20% (Condition 2), we obtain levels on the Situation Index scale indicated by the second projections in Fig. 2. Similarly, when improvements in energy consumption are equal to the amounts calculated in Analysis 3 instead of a straight 10% increase, other conditions remaining the same (Condition 3), Situation Index levels become those indicated by the third projections in the figure.

After proceeding thus through a series of analytical steps characterizing exploratory thinking, we have in Fig. 2 a very interesting picture. First, there are the improvements obtainable by vigorous and balanced health programs: that is, those which give attention to birth rates as well as death rates; second, there are the further improvements obtainable by particular efforts on the part of the people to develop their abilities and skills for dealing with agricultural, industrial and human resources; and, third, there are the improvements sometimes obtainable when there is a determined effort and when there are available significantly large amounts of investment capital either from inside or outside the country.

In the over-all picture, it may be seen that whereas a significant number of additional countries would be brought to a Situation Index level of 1 or above by the maximum or most heroic effort, improvements would fall far short of bringing countries now in the lower range to anything like that of the countries in the upper range. Using the approach developed in Paper II to show whether the individual determinants of level of living are in a favorable or unfavorable range, Table 3 has been prepared, based on the conditions visualized in Analysis 4 here, when energy consumption is

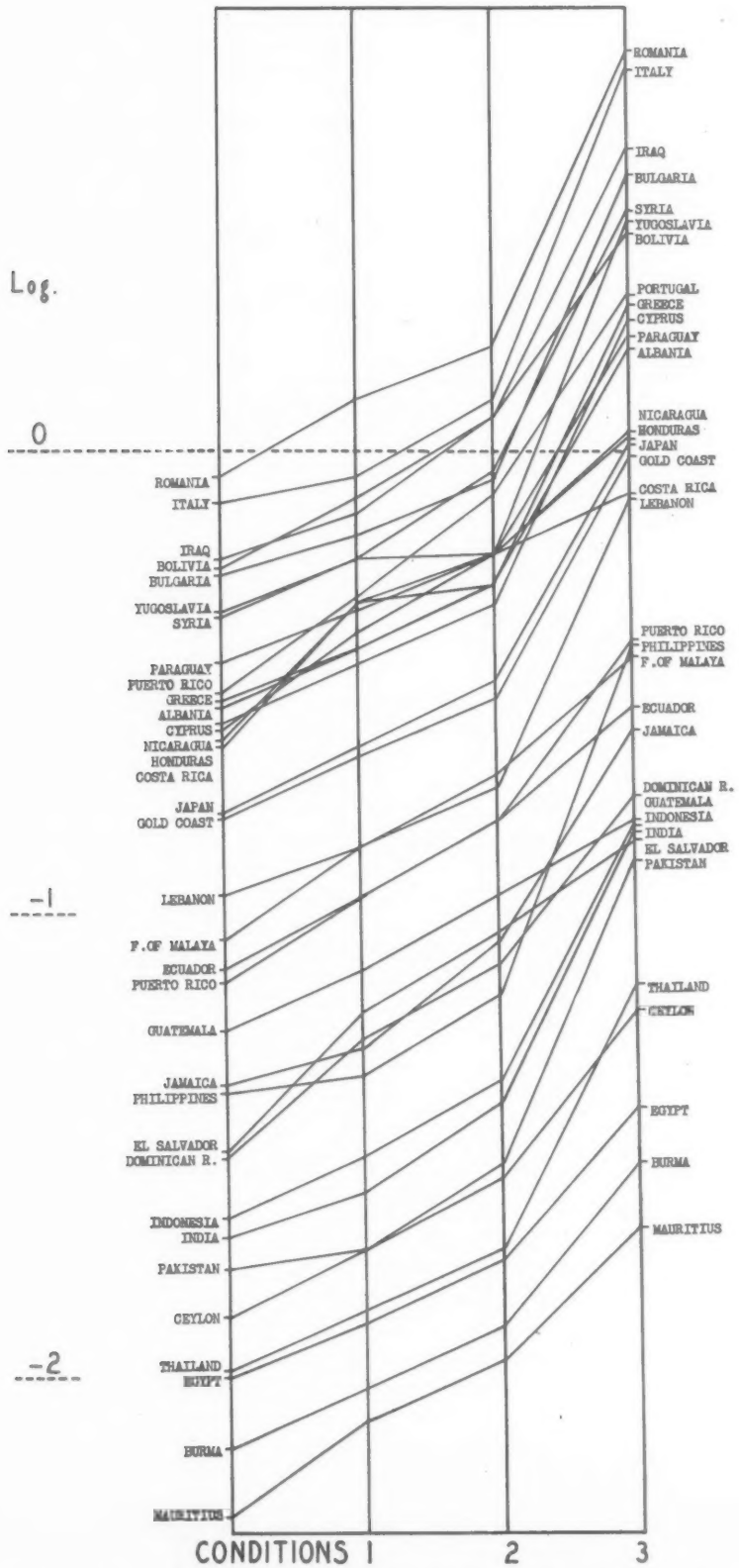

Fig. 2.—Situation Index changes resulting from arbitrarily chosen values for component determinants, Conditions 1, 2 and 3 as defined in the text.

TABLE 1.—INCREASE IN ENERGY CONSUMPTION REQUIRED FOR DIFFERENT CONDITIONS TO BRING THE SITUATION INDEX VALUE TO 1

	Industrial Energy per Capita Required to Raise the Situation Index Value to 1		
	X	Y	Z

TABLE 1.—INCREASE IN ENERGY CONSUMPTION REQUIRED FOR DIFFERENT CONDITIONS TO BRING THE SITUATION INDEX VALUE TO 1

		Present or Existing		*Industrial Energy per Capita Required to Raise the Situation Index Value to 1*				*X*	*Y*	*Z*
No.	*Country*	*Situation Index*	*Energy consumed per capita in tons coal equivalent*	*Condition A when energy only is increased*	*Condition B when B = 1.5 D = 1.0*	*Condition C when C = FAO I = +20%*	*Condition D when B = 1.5 D = 1.0 C = FAO I = +20%*	*Condition D times energy increase above existing conditions*	*Present total energy consumed in actual tons coal equivalent in millions*	*Actual increase in tons coal equivalent in millions (X × Y)*
1	Egypt	.0098	.25	26.00	9.1	18.8	6.7	27.0	4.75	130.0
3	Gold Coast	.16	.10	.65	.38	.50	.27	2.7	.37	.99
4	Mauritius	.005	.13	26.00	7.0	18.3	6.0	46.	.06	2.9
6	Costa Rica	.23	.22	1.20		1.0			.20	
8	Dominican R.	.03	.10	3.03	1.0	2.3	.71	7.1	.20	1.5
9	El Salvador	.031	.11	3.5	.95	2.4	.65	5.9	.20	1.2
10	Guatemala	.054	.12	2.2	.56	1.5	.39	3.2	.33	1.1
11	Honduras	.23	.16	.70		.26	.18	1.10	.28	.31
12	Nicaragua	.25	.10	.40	.13	.32			.10	
16	Jamaica	.043	.18	4.3	2.1	2.9	1.5	8.1	.22	1.8
17	Puerto Rico	.071	.60	8.5	3.5	5.9	2.4	4.0	1.30	5.2
19	Bolivia	.60	.12	2.0		.14			.30	
23	Ecuador	.076	.12	1.6	.50	1.1	.34	2.8	.38	.92
24	Paraguay	.35	.03	.09	.064	.066	.045	1.7	.04	.07
28	Burma	.0066	.02	3.1	1.3	2.1	.83	42.	.33	14.
29	Ceylon	.012	.10	7.8	3.9	5.6	2.1	21.	.81	17.
30	India	.02	.11	5.6	4.0	3.7	2.6	24.	40.	950.
31	Indonesia	.022	.07	3.2	1.9	2.8	1.3	19.	4.20	77.
32	Iraq	.59	.20	3.4	.25	.22			.96	
34	Japan	.16	.89	5.4	3.8	3.9	2.7	3.0	74.	230.
35	Lebanon	.11	.22	2.0	.31	1.5	1.0	4.7	.28	1.3
36	Pakistan	.017	.05	3.0	1.4	2.1	1.8	37.	3.80	140.
37	Philippines	.041	.11	2.7	1.1	2.7	1.8	16.	2.00	33.
38	Syria	.44	.22	.50	.32	.33			.75	
39	Thailand	.01	.03	2.9	1.8	2.00	1.2	41.	.50	20.
40	Cyprus	.26	.31	1.2	.75	.63	.56	1.8	.13	.23
41	F. of Malaya	.089	.41	4.6	1.4	3.3	1.0	2.5	2.	5.
42	Albania	.28	.30	1.1	.56	.78	.41	1.4	.33	.46
45	Bulgaria	.54	.30	.55	.40	.42			2.10	
52	Greece	.29	.27	.93	.62	.66	.45	1.7	2.	3.4
56	Italy	.78	.82	1.1	.96				38.	
61	Portugal	.30	.32	1.1	.59	.62	.35	1.1	2.7	2.9
62	Romania	.89	.46	.52					14.	
67	Yugoslavia	.45	.38	.84	.51	.86	.51	1.4	6.40	8.6

B = birth rate; D = death rate; C = caloric intake; I = income; FAO = Food and Agricultural Organization 1960 target.

TABLE 2.—INCREASE IN ENERGY CONSUMPTION REQUIRED FOR DIFFERENT CONDITIONS TO RAISE THE SITUATION INDEX VALUE 10 TIMES

		Present or Existing		*Industrial Energy per Capita Required to Raise the Situation Index Value 10 Times*				*X*	*Y*	*Z*
No.	*Country*	*Situation Index*	*Energy consumed per capita in tons coal equivalent*	*Condition A when energy only is increased*	*Condition B when B = 1.5 D = 1.0*	*Condition C when C = FAO I = +20%*	*Condition D when B = 1.5 D = 1.0 C = FAO I = +20%*	*Condition D times energy increase above existing conditions*	*Present total energy consumed in actual tons coal equivalent in millions*	*Actual increase in tons coal equivalent in millions (X × Y)*
1	Egypt	.0098	.25	2.5	.91	1.8	.65	2.5	4.7	12.
3	Gold Coast	.16	.10	1.0	.54	.77	.41	4.1	.37	1.5
4	Mauritius	.005	.13	1.3	.35	.99	.31	2.3	.06	1.4
6	Costa Rica	.22	.27	2.7	.41	2.3	.30	1.2	.20	.24
8	Dominican R.	.03	.10	1.0	.31	.69	.22	2.2	.20	.43
9	El Salvador	.031	.11	1.1	.29	.76	.21	1.9	.20	.37
10	Guatemala	.054	.12	1.2	.31	.86	.21	1.8	.33	.57
11	Honduras	.23	.16	1.6	.60	1.1	.41	2.6	.22	.56
13	Nicaragua	.25	.10	1.0	.33	.82	.23	2.3	.10	.23
16	Jamaica	.043	.18	1.8	.90	1.2	.63	3.5	.22	.50
17	Puerto Rico	.071	.60	6.0	2.5	4.2	1.7	2.8	1.3	3.7
19	Bolivia	.60	.12	1.2	.54	.89	.34	2.8	.30	.85
23	Ecuador	.076	.12	1.2	.38	.83	.23	1.9	.38	.73
24	Paraguay	.35	.03	.30	.21	.22	.15	5.1	.04	.21

28	Burma	.0066	.02	.20	.089	.14	.055	1.8	.33	.60
29	Ceylon	.012	.10	1.0	.40	.72	.25	2.5	.81	2.0
30	India	.02	.11	1.1	.77	.71	.51	4.6	40.	180.
31	Indonesia	.022	.07	.70	.41	.48	.28	4.0	4.2	17.
32	Iraq	.59	.20	2.0	1.5	1.3	.96	4.8	.96	4.6
34	Japan	.16	.89	8.9	6.2	6.4	4.5	5.0	74.	370.
35	Lebanon	.11	.22	2.2	1.5	1.7	1.1	5.1	.28	1.4
36	Pakistan	.017	.05	.50	.45	.34	.26	5.2	3.8	20.
37	Philippines	.041	.11	1.1	1.1	.72	.72	6.6	2.0	13.
38	Syria	.44	.22	2.2	1.4	1.4	.92	4.2	.75	3.1
39	Thailand	.01	.03	.30	.18	.22	.14	4.5	.50	2.3
40	Cyprus	.26	.31	3.1	1.9	1.6	1.4	4.6	.13	.60
41	F. of Malaya	.089	.41	4.1	1.3	2.9	.90	2.2	2.0	4.4
42	Albania	.28	.30	3.0	1.6	2.2	1.1	3.6	.33	1.2
45	Bulgaria	.54	.30	3.0	2.2	2.3	1.6	5.5	2.1	11.
52	Greece	.29	.27	2.7	1.8	1.9	1.3	4.9	2.0	10.
56	Italy	.78	.82	8.2	7.5	5.4	4.9	5.9	38.	220.
61	Portugal	.30	.32	3.2	1.9	1.9	1.1	3.3	2.7	8.9
62	Romania	.89	.46	4.6	3.1	3.5	2.4	5.2	14.	72.
67	Yugoslavia	.45	.38	3.8	2.3	3.9	2.2	5.7	6.4	36.

B = birth rate; D = death rate; C = caloric intake; I = income;
FAO = Food and Agricultural Organization 1960 targets.

TABLE 3.—RANGE VALUES INDICATING SIGNIFICANCE OF TANGIBLE IMPROVEMENTS

		A — *Present conditions (Paper 2, Table 3)*				*B* — *B = −25%; D = 1.00; C = FAO; I = +20%; E as under Analysis 3*			
No.	*Country*	2^P+2^D*	$N(2^P+2^D)$**	*CEI***	*CEI***** / $N(2^P+2^D)$	$2'+2^D$	$N(2^P+2^D)$	*CEI*	*CEI* / $N(2^P+2^D)$
1	Egypt	5	5	5	5	4	5	4	5
4	Mauritius	5	5	5	5	5	5	5	5
29	Ceylon	5	5	5	5	3	4	5	5
9	El Salvador	5	4	5	5	5		5	4
16	Jamaica	4	5	5	5		4	4	4
17	Puerto Rico	5	5	4	5	4	3	3	4
8	Dominican R.	5	3	5	5	3		5	4
41	F. of Malaya	5	3	5	5	4		4	4
61	Portugal	3	3	4	4			3	
10	Guatemala	5		5	5	5		5	4
31	Indonesia	3		5	5			5	4
39	Thailand	3		5	5			5	5
28	Burma	3		5	5	3		5	5
6	Costa Rica	5		5	4	5		4	4
11	Honduras	5		5	4	3		5	3
13	Nicaragua	5		5	4	3		5	3
23	Ecuador	5		5	4	4		5	4
19	Bolivia	4		5	4	3		5	3
38	Syria	3		5	4			4	3
40	Cyprus	3		5	4			3	3
42	Albania	3		5	4			3	3
3	Gold Coast	3		5	4			5	4
67	Yugoslavia	3		4	4			3	3
30	India		3	5	5			5	4
34	Japan		5	4	4		5		3
35	Lebanon		4	5	4		3	3	4
56	Italy		3	3	4		3		3
36	Pakistan			5	5			5	4
37	Philippines			5	5			5	4
24	Paraguay			5	4			5	3
32	Iraq			5	4			4	3
52	Greece			5	4			3	3
45	Bulgaria			4	4			3	3
62	Romania			4	4				3

* Total fertility. ** Population pressure. *** Economic development. **** Situation Index.

that calculated in Analysis 3. By comparing the range values of Part B with those in Part A of the table, it is seen that noticeable improvements are obtained along the line, but that after what may be regarded as the maximum effort, some of the countries will remain in a generally unfavorable condition. This means that in some cases the existing population pressure is so high, or economic developments so low, that phenomenal efforts would be required to lift countries out of the unfavorable range. The undertakings would be as vast as opening up desert regions by irrigation sufficiently large to cause an actual reduction in population density, as achieving a decrease in population growth over a period of time, or as developing an industrial economy in countries that at present have almost exclusively an agricultural economy.

ANALYSIS 5. Of particular interest is what will happen in the over-all picture as countries now in the upper range continue with efforts to improve their lot at the same time that countries in the lower range make an effort in the same direction; also, what kinds of developments may cause countries in the upper range to be pulled downward on the scale.

In the light of information already presented, tables and charts are not needed to answer these questions. With respect to the first, it is plain that where population pressure is not high and a good level of living has already been achieved, effort can be concentrated directly on further development of the educational, technical and natural resources, rather than be absorbed in dealing with subsistence. Without doubt, the effort in such cases would be far more rewarding than similar amounts of effort where there exist the handicaps of high fertility, high density and low economic development. In the United States, energy consumption is already 7.84 tons coal equivalent per capita which is as much as 150 times that in various other countries; agriculture is technically well developed and highly mechanized; health, educational and scientific facilities are advanced; and population density is not yet excessive. These are conditions which favor more rapid development. It seems safe to predict that unless some effective policy is evolved to assure more uniform development, the trend for some time to come will be toward increasing the present discrepancies.

With respect to the second question, it is obvious that where economic development is advanced and population density high, any increase in fertility or even of population level will of necessity have to be compensated for by further economic development if level of living is not to fall. Where agricultural development is already near maximum, as in countries in Western Europe, population increases in such cases would have to be counterbalanced by industrial development except in so far as income can be increased by other means. Accordingly, it is plain that in economically more advanced countries where density is high, population increases will be serious matters if there are not opportunities for further industrialization to go along concurrently. Since fertility continues to be significantly high in a number of countries that are economically advanced, it is to be expected that in time more will come into this precarious and uncertain range.

ANALYSIS 6. Keeping attention focused primarily on the problems of less developed countries, it is important to consider the inital efforts most influential in achieving economic improvement and something of their costs: in effect, to compare the health dollar

(or other monetary unit) with the economic development dollar in terms of how much improvement each may be expected to provide.

Here it will be convenient to put cost analysis on a per capita basis the same as was done for the various determinants. Taking income first, adding one dollar per year per person obviously would not change the general picture significantly, although such an addition would not be inconsequential in countries where per capita income is less than $100 per year. Taking caloric supply second, it is equally obvious that one dollar additional per person for improving agricultural productivity would not change the situation greatly if used for providing more fertilizer and more machinery, but again the addition would not be inconsequential, particularly if put into better breeding stock, both plant and animal, or put into technical information that could be used generally. The picture is much the same in the case of industrial energy. In countries with 100 million population or more, one dollar per person would go a long way toward providing sources of electric power, but one dollar per person would be as of nothing when it comes to purchasing the equipment needed on farms and in factories for utilization of such power when available.

With respect to the cost of improvements resulting from public health, the outlook is different, due mainly to the fact that many people can benefit from measures which are not too costly; also, to the fact that such measures go a long way toward lifting depressed people from a state of apathy to one of stimulus and motivation. Incentive comprises the basis for advancement and it is often set off by successful demonstrations in education, agriculture, industry and health, but health has a special significance in that it involves improvements in physical well-being which may be felt very quickly. It is conceivable that accomplishments no greater than indicated by the first projections in Fig. 2 would trigger off incentive sufficient to open the way for numerous other developments of some magnitude, especially if accompanied by what may be called inspired leadership, one which creates a fervor for improvement.

Primary elements for a balanced health program can be visualized as: (1) insect control by DDT or agents similar to reduce malaria and dysentery mainly, (2) vaccinations to reduce other infectious diseases, and (3) fertility management by various acceptable means such as attention to the natural rhythm of ovulation or the use of carefully chosen spermicidal tablets to be applied in the vagina at the time of coitus. A million dollars for each million people would be significant in providing such innovations. Estimates indicate, in fact, that if such minimum health features were made available as a public service on a mass basis, they might easily be provided for half or even a quarter this amount.

It must be added that improvements in nutrition are also important in overcoming lethargy and indifference, a feature which is largely a matter of health but one dependent to a considerable extent on agriculture. Costs of nutritional improvements therefore are involved mainly in the costs of agriculture.

Granting that health benefits vary directly with the amounts invested in them, let us consider what might be the consequences of the minimum provisions mentioned. It is well demonstrated that proper application of DDT results in a precipitous decline of infant mortality and in a significant reduction of morbidity and mortality in the adult population. Similarly, inocu-

lations for smallpox and other diseases that constitute a problem and such as may be amenable to control by the method, result in additional improvements of the same types. Acceptable and statistically effective fertility management then would provide the necessary balance. It would enable parents to approximate the number of children they want, which, it may be assumed, would in most cases be a number for which there are prospects of dignified support. Taking into account the natural desire of people everywhere to be healthy and to have healthy families, it is to be expected that in general they would avail themselves of disease and fertility management opportunities when such exist. Self sufficiency in the family has its appeal over and above sufficiency provided through supplements by the state or otherwise. Because of the technical potentialities for disease and fertility management, minimum health programs in overcrowded and as yet underdeveloped countries might safely be relied upon to reduce greatly the wastage of human resources, and at the same time reduce the poverty and degradation caused by overlarge families. For a more extended discussion of this subject see Reference 1.

Disease control and fertility control, it must be recognized clearly, operate in different directions, a condition allowed for in a somewhat unique manner in the expression for total fertility in the Situation Index formula. Lessening of high fertility is in phase with improvement, and lessening the frequency of death as such is in opposition to it. By all standards of advancement, however, death control is in keeping with the best human objectives and without doubt will continue to be aided in every way possible by people generally. Any other course would be defeatist in the extreme. Now that populations have grown so very large and that population density is already high in many countries, balanced health undertakings are of growing importance. Within the scope of such undertakings is the opportunity to take advantage of the general human desire for total family health, achievable in considerable degree by means of the educational and promotional features automatically inherent in minimum balanced health programs. Developed in the right way, such programs can be utilized to break the grip of apathy and indifference.

At this point, let us return to the underlying premise that level of living varies inversely with the number of people making demands for the materials needed for life which are available. Often the point of view is advanced that greater economic, military and over-all national strength comes from larger populations; in fact, the largest possible. Our premise is not in conflict with this view except it assumes that people are assets to themselves, to their community and to their country only when healthy and solvent. Indiscriminate reproduction easily results in offspring for which there is little opportunity to avoid disease and destitution. Going further, efforts for improvements in agricultural and industrial productivity in countries with high population density, and which are unattended by any helpful guidance on matters of fertility, often are offset by population increases with the consequence that the subsistence equilibrium is little modified. So far as economic, military and national strengths are concerned, adapting fertility to agricultural and industrial productivity assumes a place of importance along with control of disease. The two together comprise the basis for increasing strength.

Of particular significance is the fact that fertility appears to act as a power

function, whereas the factors of population density and economic development operate more as natural functions. Indications are that changes in population level, either increases or decreases, affect level of living far more than similar numerical changes in the other categories, particularly in economically less developed countries. It is this feature, more than any other that makes health measures so significant.

All things considered, it is apparent that investments in health, especially during early phases of economic development, are likely to have greater influence than investments of similar amounts in other types of improvement. The information assembled points strongly to the idea that emphasis should be on carefully designed health programs as a point of departure in planning and promoting newer improvement undertakings.

Comments. Findings here accent the significance and importance of fertility and at the same time the necessity of having population growth in phase with availability of resources, if level of living and the national strength are not to deteriorate. It has been pointed out that reduction of birth rates and reduction of death rates operate antagonistically in the growth mechanism, and that the smaller the number of people making demands for existing materials, the higher the level of living. Whereas this picture is reasonable and apparently correct for any given level of existing materials, it does not necessarily follow that lowering of fertility will invariably result in improvement of living conditions, inasmuch as productivity becomes modified by changes in numbers of people. As is well known from practical experience, there are situations in which levels of living have improved as a consequence of population increase. These are situations in which per capita productivity is raised by efforts of the newer elements of population, elements which may result from increased birth rates, decreased death rates or immigration. Per capita productivity, which is influenced and to a large extent governed by the limits of resources and by the abilities and skills of people to use resources, must be evaluated as fully as fertility.

In the Situation Index formula, decline in death rate alone causes a rise in Situation Index values, but declines as a consequence of health programs result in a saving of wasted fertility, causing this increment to become absorbed in the actual fertility and thus to continue contributing to population pressure. Level of living, in such instances, is maintained only when productivity is caused to keep pace or to exceed. Within the scope of the formula also is opportunity for the level of living index to rise even when population is increasing, which is a requirement when per capita productivity is actually raised by newer population increases. These provisions give consistency to the over-all approach and enable a logical analysis.

Through development of the Situation Index formula and its application thus far, we have identified determinants, set forth a picture of operational behavior and obtained impressions of relative effects of interacting elements in abstract terms. In subsequent studies, attention will be given to the weighting of component determinants, in which case values for the different expressions will come to have more concrete meaning.

In closing, it is necessary to stress again that analyses making use of the Situation Index formula cannot be more reliable than the basic data employed or the applicability of underlying assumptions. We believe the model, as

conceived, has meaning and is useful for evaluation purposes. In any case it is available for testing and for further elaboration if needed.

Summary. 1. Utilizing six analytical procedures, calculations and estimates have been made of requirements for advancing or maintaining levels of living in countries and territories with different degrees of development, primarily those little developed thus far. Consideration was given first to specifically defined theoretical goals by means of which more realistic objectives were derived.

2. Findings indicate that population density and rates of population increase are already so high in many economically less-developed countries that attempts to raise levels of living to no more than the present intermediate range would be practically impossible of achievement if undertaken by agricultural and industrial improvements alone, and further, that disease control unattended by guiding ideas on fertility matters adds to the problem, tending to neutralize gains that are made.

3. Analysis of the operating mechanism showed health programs to be of particular significance, since they affect birth and death rates, and since these, in turn, act as power functions in affecting level of living, whereas other measures influence factors that act more as normal functions.

4. It became apparent that health programs have the possibility of being used to break the grip of apathy and indifference and also to assure that gains for improvement will be lasting gains.

5. Conclusions were that emphasis should be on carefully planned and well balanced health developments as a point of departure in promoting newer improvement undertakings, and that investments in health during early phases are likely to provide greater returns than equivalent investments in other measures.

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(Interlingua on page 697)

THE RECTAL ABSORPTION OF MERCAPTOMERIN LABELED WITH HG^{203}*

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In the therapy of fluid retention states it has been customary to reserve the use of organic mercurial diuretic agents until clinical evidence of edema was present. Recently, however, Olson and Seager[3] have suggested that small, repeated doses of mercurials should be given regularly to prevent the development of edema, much as digitalis is administered in a maintenance dose. Such an approach requires a simple method for the administration of the mercurial diuretic agent. Although it is recognized that the most reliable method of administration is by parenteral injection, this is far from practical for routine use. A mercurial diuretic agent which has recently been introduced in suppository form has been shown to elicit a diuretic response clinically and to produce no local rectal irritation[2]. However, no data are currently available regarding the absorption of this organic mercurial compound when administered *per rectum*.

The purpose of the present study was to determine, in subjects with and without edema, the absorption, blood concentration and urinary excretion of mercury administered as a single suppository of mercaptomerin sodium (Thiomerin), which had been labeled with Hg^{203}.

Material and Methods. Suppositories** were made up in a cocoa butter base to contain 0.5 gm. of mercaptomerin sodium (equivalent to 165 mg. of mercury) and 500 microcuries of radioactivity as Hg^{203}. Single suppositories were administered to a total of 13 hospitalized patients, 8 of whom were convalescent from various diseases and were free of visible edema, and 5 of whom were suffering from cardiovascular disease with chronic peripheral pitting edema. None of the subjects had any demonstrable abnormality of the gastrointestinal tract. All patients were at bed rest and were on a regular or low-salt hospital diet. Fluids were given without restriction.

Prior to its administration, each suppository was weighed and its radioactivity content assayed. It was then inserted deep into the rectum with the gloved index finger, and the subject was requested to retain the suppository as long as possible. Initially, specimens of urine and blood were obtained every hour for the first 6 hours, and at less frequent intervals thereafter for 72 hours. When it became apparent that profound diuresis would not be induced by the administration of a

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**Hg^{203}-labeled mercaptomerin sodium suppositories were synthesized by the Wyeth Institute of Applied Biochemistry.

single suppository, specimens were obtained at less frequent intervals. Complete stool collections were attempted on the first 3 subjects studied.

ASSAY OF RADIOACTIVITY. Samples of serum and urine specimens were placed, without prior treatment in 1-dram glass vials, which were stoppered and were then placed individually in the well of a Nuclear Model DS-3 scintillation well counter for gamma ray assay. At no time were these samples subjected to temperatures higher than 75° F., so that loss of mercury through volatilization was obviated. In order to obtain a homogeneous mixture of the stool specimen, however, it was necessary to add concentrated sodium hydroxide to the material; considerable heat was thereby generated, and it is suspected that some volatilization of mercury may have occurred during this treatment.

Results. The total urinary excretion of radioactivity following the rectal administration of a single suppository containing 165 mg. of mercury as Thiomerin was low, both in the subjects with edema and in those without (Table 1). The percentages of the suppository dose recovered in the urine varied between 3.02 and less than 0.50. The highest percentages recovered, 3.02 and 2.74 respectively, were obtained from a subject convalescent from bacterial pneumonia, and a patient who had cor pulmonale and congestive heart failure with peripheral edema. These were the only 2 subjects who showed an increase in urinary volume following the administration of the suppository: the former had consecutive daily volumes of 5,261, 3,010 and 1,340 cc. (Fig. 1), and the latter, consecutive daily volumes of 2,472, 1,640 and 1,300 cc. (Fig. 2).

Each of 4 subjects with edema whose urinary excretion was less than 0.50% of the administered dose of radioactivity (Table 1) retained the suppository less than 5 hours, although none complained of local rectal irritation following its insertion. Other subjects retained the suppository at least 8 hours.

There was considerable variation in the time required for attaining the maximum concentration of radioactivity in the blood; although 12 of the maximum values were obtained within 3 to 8 hours, in one subject (J.V., Table 1) the maximum serum concentration of Hg^{203} was not reached until 12 hours after administration of the suppository.

When the maximum serum concentration of radioactivity attained was plotted against the total urinary excretion of Hg^{203} (Fig. 3), good correlation was found. Serial determinations of the urine volume and of the serum and urinary concentrations of Hg^{203} in the 2 subjects with the greatest urinary excretion of radioactivity also showed suggestive parallel relationships (Figs. 1 and 2).

Discussion. The results of the present study suggest that the absorption *per rectum* from a single suppository containing 165 mg. of mercury as Thiomerin is usually insufficient to induce diuresis. Calculations based on the specific activity of the material used reveal that a minimum of 4.5 mg. of mercury must be absorbed in order for a diuretic response to occur. It can also be similarly calculated that the maximum serum concentration of mercury attained from rectal absorption was on the order of 0.5 microgram per cubic centimeter of serum.

It is probable that the low absorption figures may be due, at least in part, to failure of some of the patients to retain the suppository long enough for maximal absorption to occur. The suppositories were administered to the subjects in the present study without prior inquiry into their bowel habits. It may be that administration of the material immediately after a bowel movement might have resulted in a longer period of contact with the rectal mucosa and, hence, in greater absorption of the Thiomerin. The results in subject J.V. suggest that maximal blood concentrations may not be attained for

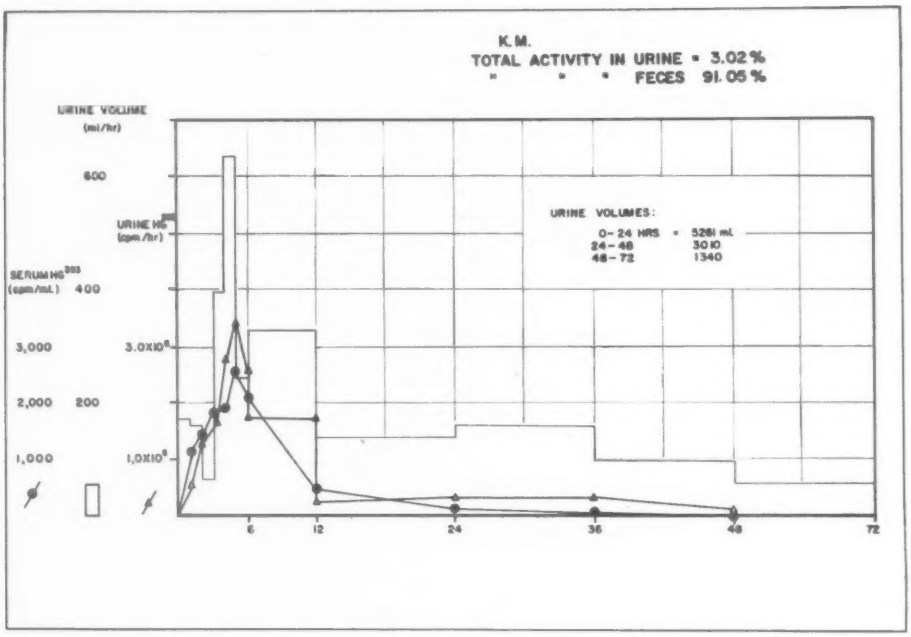

Fig. 1.—Serum and urinary radioactivity and urine volume in a subject without edema who had diuresis after one suppository of Hg^{203}-tagged mercaptomerin.

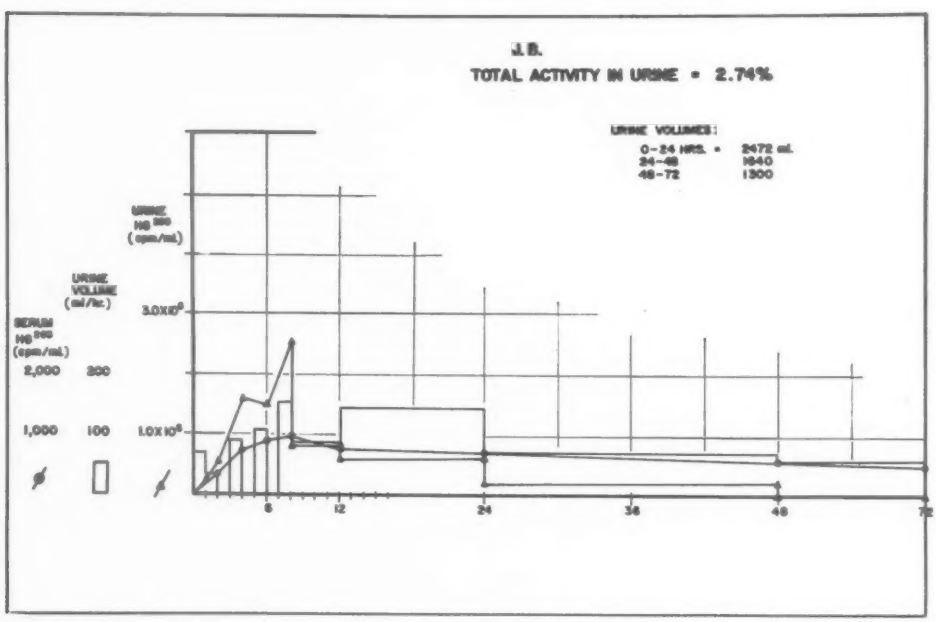

Fig. 2.—Serum and urinary radioactivity and urine volume in a subject with edema who had diuresis after one suppository of Hg^{203}-tagged mercaptomerin.

TABLE 1.—THE RECTAL ABSORPTION OF MERCAPTOMERIN LABELED WITH HG^{203}

THE URINARY EXCRETION OF RADIOACTIVITY FOLLOWING THE RECTAL ADMINISTRATION OF ONE HG^{203}-TAGGED THIOMERIN SUPPOSITORY

Subjects without Edema	K. M.	3.02*	Subjects with Edema	J. B.	2.74*
	J. V.	2.25		L. M.	< 0.50
	A. L.	1.76		L. M.	< 0.50
	A. L.	1.56		M. Y.	< 0.50
	O. T.	1.34		E. G.	< 0.50
	E. M.	0.87			
	T. C.	0.81			
	T. L.	0.20			

* Per cent of the total radioactivity administered.

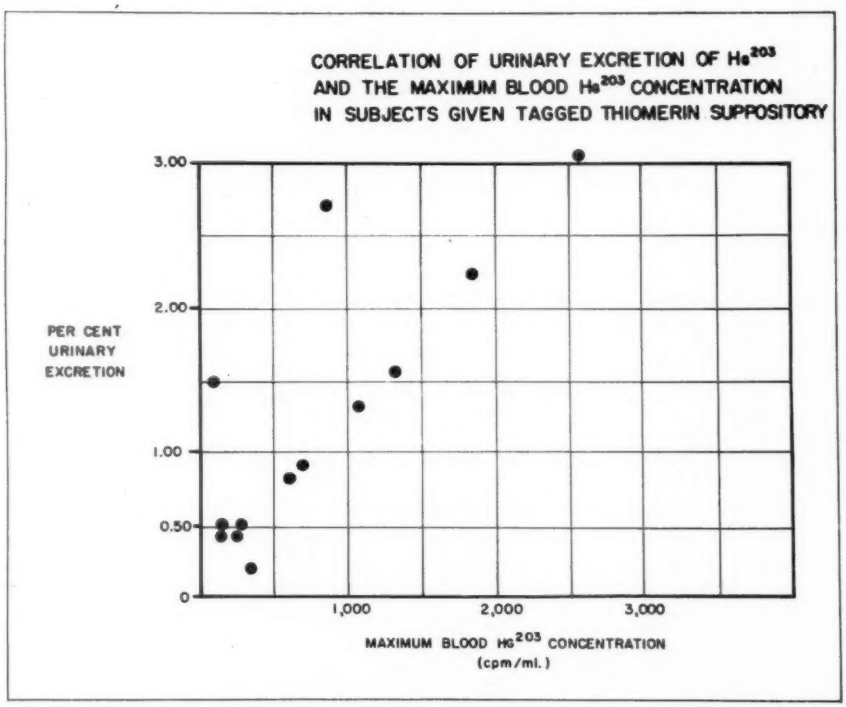

Fig. 3.—Correlation of urinary excretion of Hg^{203} and the maximum blood Hg^{203} concentration in subjects given tagged Thiomerin suppository.

as long as 12 hours after the administration of the suppository.

The correlation between the maximal concentration of Hg^{203} in the blood and the total urinary excretion of radioactivity is interpreted to be merely an expression of the magnitude of rectal absorption. Although there appears, in the 2 subjects who experienced diuresis, to be a parallel relationship between the urine flow and the blood and urinary concentrations of Hg^{203}, further studies are necessary to determine whether or not this relationship occurs regularly. Weston and his co-workers have previously demonstrated that the renal extraction of mercury follows the intravenous injection of a mercurial diuretic

agent[4]. We have previously demonstrated in rabbits the renal localization of Hg^{203}, tagged Thiomerin[1]. These observations complement those reported here and contribute further to an understanding of the mechanism of action of the mercurial diuretic agents.

A previous clinical study[2] on the use of Thiomerin in suppository form has suggested that rectal administration of this drug is effective in maintaining an adequate diuretic response if repeated doses are used; this observation suggests that, although the proportion of mercury absorbed from each suppository is small, repeated administration produces a cumulative effect.

Summary. A single suppository of mercaptomerin sodium labeled with Hg^{203} was administered to each of 13 subjects, 8 without edema and 5 with congestive heart failure and peripheral edema. Serial specimens of blood and urine were obtained and the serum concentration and total urinary excretion of radioactivity were correlated with the diuretic response. It was found that absorption of a minimum of 4.5 mg. of mercury *per rectum* was necessary to evoke diuresis. Only 2 subjects, one with edema and one without, showed a diuretic response. The maximum concentration of radioactivity in the blood, although erratic in time of appearance, correlated well with the total urinary excretion of radioactivity.

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SUMMARIO IN INTERLINGUA

Le Absorption Rectal de Mercaptomerina Etiquettate a Hg^{203}

Un sol suppositorio de mercaptomerina etiquettate a Hg^{203} esseva administrate a cata un de 13 subjectos. Inter illes, 8 esseva sin edema, e 5 habeva congestive disfallimento cardiac e edema peripheric. Specimens serial de sanguine e de urina esseva obtenite, e le concentration seral e le total excretion urinari de radioactivitate esseva correlationate con le response diuretic. Il esseva constatate que le absorption rectal de un minimo de 4,5 mg de mercuric esseva requirite pro evocar diurese. Solmente 2 subjectos, un con edema e le altere sin edema, monstrava un responsa diuretic. Le concentration maximal del radioactivitate in le sanguine esseva erratic quanto al tempore de su apparition, sed illo monstrava un bon correlation con le excretion total de radioactivitate in le urina.

THE RELATIONSHIP OF CIRRHOSIS OF THE LIVER TO HYPERTENSION: A STUDY OF 504 CASES OF CIRRHOSIS OF THE LIVER

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The differing viewpoints regarding the etiology of essential hypertension reflect an insufficient knowledge of the basic lesion. Since we have not identified this lesion, and the natural history is so confused at this time, it would be interesting to note in what circumstances hypertension does not occur. A number of investigators have commented on the absence of experimental and clinical hypertension with liver disease[1,5,8]. Recent studies of Raaschou[7] have tended to confirm these ideas when he found that the frequency and degree of hypertension was substantially higher in a control group than in patients with subacute liver atrophy who later came to postmortem examination. He concludes that hypertension could not occur in the presence of more than minimal liver damage.

In view of this report, we sought to examine the nature and frequency of hypertension in a consecutive series of cases with cirrhosis of the liver obtained from the records of St. Alexis and St. John's Hospitals in Cleveland through the years 1943–1954 inclusive. A total of 567 cases was reviewed and of these 504 proved to have a positive diagnosis of cirrhosis. The findings show that hypertension does not usually occur with cirrhosis of the liver. However, it may develop during the course of the disease under certain circumstances, such as painful stimulation or renal disease. Likewise, previous hypertension was found to reverse to normal pressure with the establishment of cirrhosis.

The acceptable cases were divided into four clinical categories based on: 1) clinical diagnosis, Group A; 2) biopsy diagnosis, Group B; 3) necropsy diagnosis, Group C. The remaining cases which had a doubtful diagnosis or inconclusive recorded evidence of the disease were tabulated to avoid error and to preserve the consecutive series. Clinical diagnosis was accepted only if two or more of the following clinical or laboratory tests, or both, were recorded: hepatomegaly of at least 3 finger breadths, alcoholic history, ascites, cephalin flocculation of at least 2 plus, retention of Bromsulphalein of 5% or more. All hospital admissions, regardless of the cause for hospitalization, were reviewed. Only admitting blood pressures with the patient in the recumbent position were used for the purpose of this study.

Observations. Analysis of the average blood pressures of 567 cases at the last admission showed those of the clinical group to be 134/83; of the biopsy group, 133/81; and of the necropsy group, 131/79. There were 64 cases of doubtful diagnosis or insufficient recorded evidence of cirrhosis with an average blood pressure of 154/84. The age distribution of all groups was similar (Table 1).

In Fig. 1 is presented the frequency distribution of the blood pressure and age groups of the cirrhotic patients. Inspection of Fig. 1 (cross-hatched areas) reveals that there were 90 cases with systolic blood pressure over 150

*At present on active duty with the 4450th Base Hospital, Langley Air Force Base, Virginia.

TABLE 1.—SUMMARY OF 504 CASES OF CIRRHOSIS OF THE LIVER WITH REFERENCE TO HYPERTENSION

	Admissions		*Sex*		*Blood Pressure*	
Group	*Type*	*Total*	*F*	*M*	*Reading Average*	*Age Av. Yrs.*
Clinical diagnosis group	Last admission	374	96	278	134/83	55
	Total admissions	898			120/73	
Biopsy diagnosis group	Last admission	53	25	28	133/81	52
	Total admissions	110			138/81	
Necropsy diagnosis group	Last admission	77	32	45	127/72	54
	Total admissions	166			135/77	
Totals	Last admission	504	153	351	131/79	54
	Total admissions	1174			131/77	

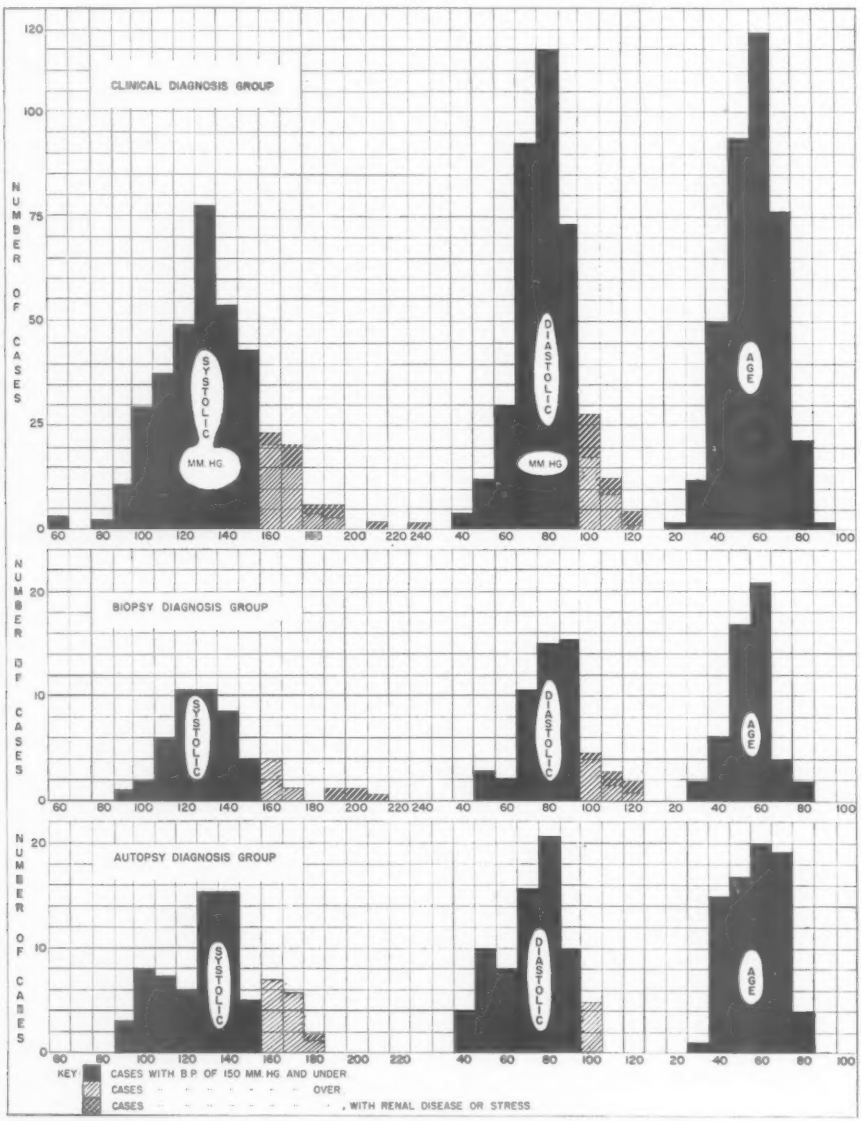

Fig. 1.—Frequency distribution of 504 cases of cirrhosis of the liver with reference to last admission blood pressure, age and number of cases in the clinical, biopsy and necropsy groups.

and 60 cases with diastolic blood pressure over 90. This includes 13 cases in which admitting blood pressures were influenced by various distressing stimuli, and 14 cases in which renal disease coexisted. The details of these will be summarized below. There remain 36 cases of hypertension in which diastolic pressures of 100, 110 and 120 were exceeded.

TABLE 2.—COMPARISON OF 504 CASES OF CIRRHOSIS WITH A NORMAL GROUP SHOWING AGE AND BLOOD PRESSURE DISTRIBUTION

Age group	20–29	30–39	40–49	50–59	60–69	70–79	80–89	90–99
Number of cases	2	22	86	125	167	80	19	1
Average blood pressure last admission	110/80	138/82	114/75	133/79	134/78	137/79	134/77	125/75
Hypertension—lower limit Master*	140/90	145/95	165/100	175/106	190/110			
Normal range blood pressure upper limit—Master*	140/90	145/92	155/96	170/100	175/100			

* Master *et al.*[5]

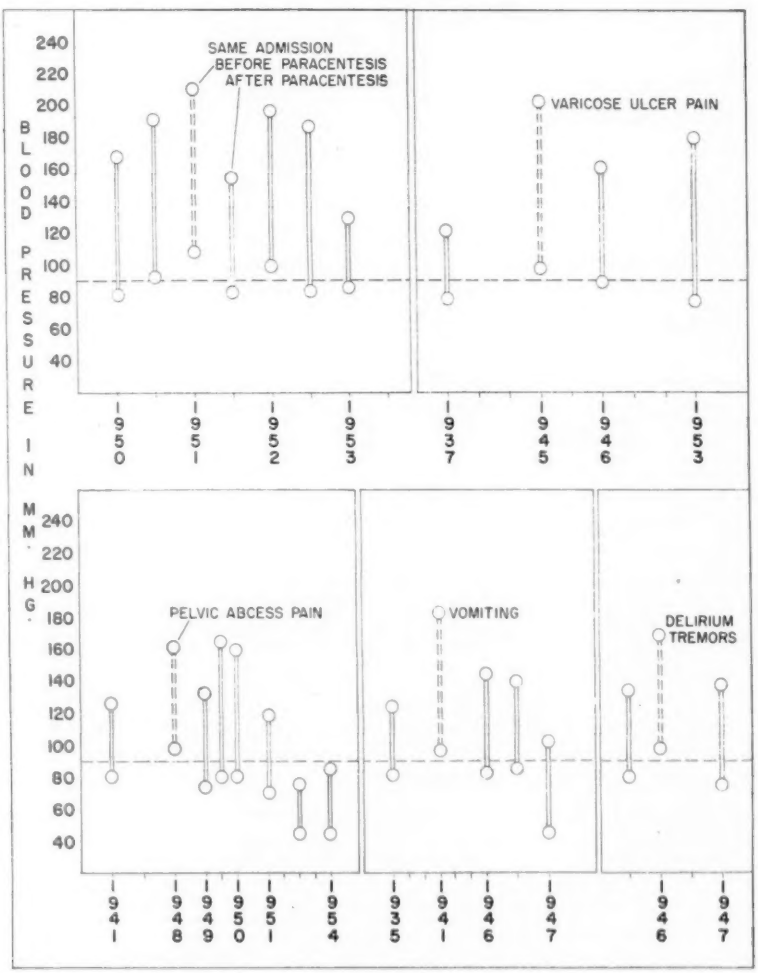

Fig. 2.—The effect of stress on cirrhosis.

The average blood pressure for each age group in our series of cirrhosis (Table 2) shows that the absence of progressive corresponding increase in blood pressure is comparable to the study of normal individuals reported by Master[3]. Blood pressure averages by Master and Symonds[4], for healthy males show that our figures are lower in the cirrhotic group. In the 40- to 70-year group where sufficient numbers are present, it is apparent that the mean blood pressures are lower in the cirrhotic patients. Of 34 cases in which stress stimuli were recorded, 18 were discarded because of inadequate blood pressure data. In the remaining 16, such stimulation produced a rise in blood pressure as seen in normal persons. Five representative examples are presented in Fig. 2. It would appear that this neurogenic painful stimulation is physiological rather than pathological, since subsequent blood pressures were not elevated.

Renal mechanisms may induce hypertension in the presence of cirrhosis as shown in Table 3. Every case of renal disease occurring in a cirrhotic during this study is here recorded. Blood pressure readings before the development of renal disease were not available. In case number JA 5, a blood pressure of 160/90 is recorded three years before death. Case AA 27 possibly does not demonstrate hypertension because the patient had undergone nephrectomy prior to the recording of the blood pressure.

The effect of advancing cirrhosis in lowering pre-existing hypertension is reviewed in all cases (see Table 4) in which adequate data were available. It would appear first, that hypertension was present when liver damage was already demonstrable in 9 cases and fell to normal at the time the A/G ratio reversed in 6 of these patients.

Discussion. This study confirms that hypertension is less likely to occur in cirrhotics than in normal individuals. The renal and neurogenic mechanisms capable of elevating the blood pressure remain intact with this disease, as illustrated by the cases of renal disease coexisting with hypertension and stressful stimuli producing hypertension. That some cases of hypertension can coexist with at least moderate hepatic disease but tend to disappear as hepatic failure advances is shown by the finding of 22 of the 504 cases of hypertension with diastolic blood pressures exceeding 110 and by the observance of 6 cases in whom the blood pressures fell under observation as the liver disease advances to the point of A/G ratio reversal. On the other hand, mildness of hepatic insufficiency cannot account for the presence of hypertension in the patients with coexisting renal disease, since 2 of the 4 cases with recorded A/G ratios had such severity as to exhibit reversal of the A/G ratio. This tends to cast doubt on the theory that hypertension is less frequent in cirrhosis because the damaged liver is unable to form the protein substrate on which renin acts. It can, however, be agreed that the coexisting renal disease was not the cause of the observed hypertension and that in these cases, as in the other with renal disease, a nonrenal mechanism was operative.

The cases in which the blood pressure fell as the liver failure advanced, are the most impressive evidence of the dependence of "essential" hypertension on adequate hepatic function. It could be argued that their pressure declines were the result of progressive malnutrition, cachexia or salt restriction. However, there is no evidence from the clinical records to indicate that the individuals whose blood pressure fell to near normal were on a severely restricted sodium intake.

TABLE 3.—CHRONIC RENAL DISEASE WITH CIRRHOSIS OF THE LIVER AND HYPERTENSION

Case	*Age*	*Sex*	*Last Admission Blood Pressure*	*Renal Pathology*
JC—2	39	M	210/120	Pyelitis
AB—23	54	M	192/116	Glomerulonephritis
AC—120	66	M	170/110	Nephritis
JC—141	63	M	174/106	Non-functioning kidney with stone
JC—24	63	F	174/106	Ureteral stone with pyelonephritis
JC—142	47	M	170/100	Uremia
JA—31	63	M	150/100	Arteriolar nephritis cancer kidney
JC—215	66	M	138/100	Uremia
JC—133	67	M	180/90	Glomerulonephritis
AC—77	76	M	155/90	Nephrosis
AA—4	76	F	144/80	Nephrosis
JA—5	37	F	130/70	Nephrosis
AA—27	58	M	120/70	Pyelonephritis with nephrectomy
AA—17	50	M	110/70	Glomerulonephritis

TABLE 4.—REVERSAL OF HYPERTENSION

Case	*Age*	*Year*	*B.P.*	*Liver Enlarged*	*Ascites*	*Cephalin Flocculation*	*B.S.P.*	*Icteric Index*	*A/G Ratio*	*Remarks*
J.C.—61	56	'35	160/100	0	0	..	..	..	..	Bursitis
		'41	210/130	0	0	..	..	..	..	Appendectomy
		'51	190/90	2+	0	..	..	..	..	Hypertensive car-
		'52	140/90	2+	0	4+	..	..	5.6/1.9	diovascular disease
		'52	166/100	0	0	3+	..	..	4.1/2.1	Cirrhosis of liver
		'53	124/78	3+	0	2+	..	..	3.7/2.2	
J.B.—10	60	'36	198/108	0	0	..	..	..	..	Hysterectomy
		'48	144/96	0	0	..	..	..	..	HCVD + asthma
		'51	140/72	0	0	..	..	..	..	Appendectomy
J.B.—16	47	'40	180/110	0	0	..	..	..	..	Barb. intox.
		'45	160/90	0	0	..	..	..	..	Bursitis
		'53	150/90	2+	0	0	0%	..	3.1/3.8	Chronic cholecys-
		'54	148/85	1+	0	0	..	..	..	titis. Biopsy: fatty metamorph.
J.C.—26	51	'46	164/110	0	+	..	..	12	..	
		'47	220/130	1+	+	0	..	45	4.1/1.8	
		'49	168/120	3+	+	4+	..	19	2.4/4.1	
		'49	110/80	4+	+	..	..	16	..	
		'50	138/76	4+	+	0	..	25	3.0/2.3	
		'50	110/70	4+	+	4+	..	14	2.4/4.1	
		'51	138/86	4+	+	..	..	..	..	Expired
J.C.—66	59	'52	160/110	0	0	0	0%	..	3.8/3.2	HCVD
		'52	132/90	2+	0	..	..	9.1	4.2/3.0	Paget's disease
		'53	100/80	4+	0	4+	..	..	2.7/4.1	
J.C.—77*	59	'50	160/100	4+	0	4+	..	10	..	
		'52	142/80	4+	0	1+	..	20	..	
J.C.—97*	52	'36	154/100	0	0	..	..	..	..	Surgery
		'52	132/78	4+	0	4+	0%	17	3.8/3.8	Cirrhosis
J.B.—23*	60	'48	210/100	1+	0	+	..	7	4.5/3.9	Biopsy: fatty
		'48	132/74	1+	0	0	..	15	3.3/4.4	metamorph.
J.A.—16*	62	'50	194/110	..	..	..	..	..	..	
		'52	120/50	..	..	..	..	..	..	

*Questionable reversal of hypertension.

Raaschou[6] made similar observance in hypertensive patients who developed severe epidemic hepatitis. Furthermore, cardiac and renal disease leading to similar degrees of cachexia is rarely accompanied by marked fall in blood pressure 1 to 6 years prior to death. In carcinoma[2], however, cachexia may be related to blood pressure fall, but this conclusion is by no means certain. The presence of an abnormal globulin being necessary for the persistence of essential hypertension must be considered, since there was a coincidental reversal of the A/G ratio, or rather that an abnormal globulin has the ability to block a hypertensive substance.

This clinical study confirms the pathological studies of Raaschou, that a normal or at most slightly impaired liver function is a necessity for arterial hypertension in man. Our investigation further shows that the hypertension, which is seen in the cirrhotics following stressful stimulation should be considered as physiological rather than pathological. Finally, it is demonstrated that established hypertension may be reversed to normal blood pressure levels with the development of cirrhosis. During this reversal, coincidental reversal of the A/G ratio was noted. The question of an abnormal globulin in maintaining or blocking "essential" hypertension is raised.

Conclusions. On the basis of an analysis of the records of 504 cases of cirrhosis of the liver, it is concluded that 1) Hypertension does not usually occur in the presence of cirrhosis.

2) Hypertension may exhibit itself in cirrhotics with the development of renal disease.

3) Stressful stimulation may produce temporary hypertension in cirrhotics.

4) Established hypertension was found to be reversed to normal pressure with the onset of cirrhosis.

5) Coincidental reversal of the A/G ratio was seen with return of hypertension to normal range.

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(Interlingua on page 659)

A SIMPLE MICROMETHOD FOR DETERMINATION OF BILIRUBIN IN PLASMA

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Repeated determinations of plasma or serum bilirubin are of great importance in the diagnosis and treatment of jaundice in the neonatal period, especially in erythroblastotic infants. Venipuncture as a method of collecting sufficient blood may be hazardous in this age group. The alternative method up to now has been to attempt to secure the blood in pipettes or small tubes from the heel or toe and then to attempt separation of the serum in an ordinary centrifuge. This often proves to be a frustrating experience for the blood so collected in a dropwise manner frequently clots before there is enough in the pipette or tube to make separation worthwhile. The following method affords both prompt collection and easy separation, and enables us to give a report on the bilirubin level within 45 minutes of receipt of a

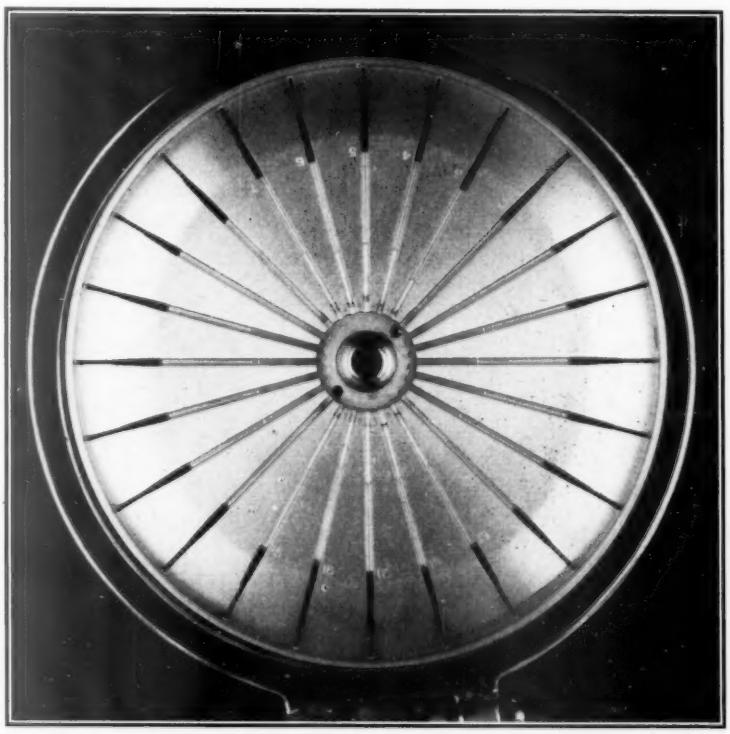

Fig. 1.—Arrangement in hematocrit centrifuge following centrifugation.

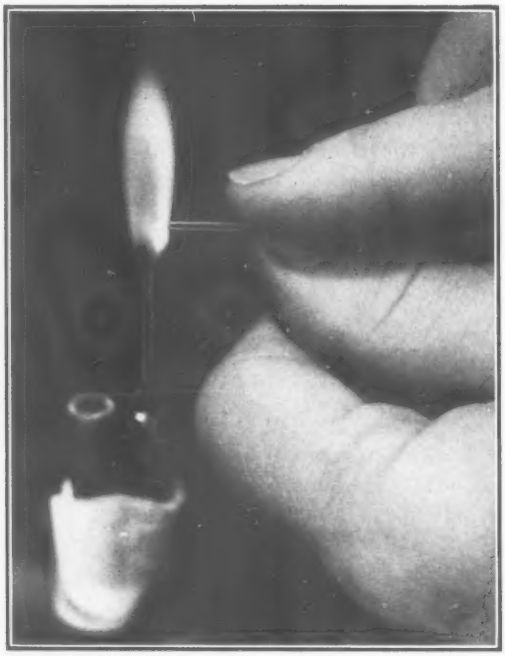

Fig. 2.—Sealing of test capillary tubes on microburner flame.

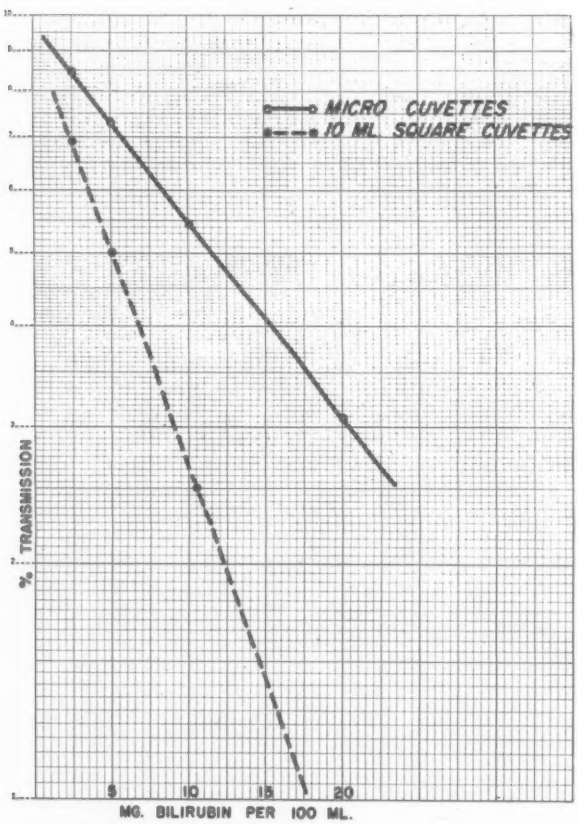

Fig. 3.—Calibration curve for translation of percentage of transmission to mg. of bilirubin. Figure also shows difference between curve obtained with microcuvette and curve obtained with standard cuvette. Reason for these differences are not clear.

request for this determination. The equipment utilized is part of many hospital laboratories today or is commercially available.

Materials and Methods. (1) Coleman Jr. Spectrophotometer, Model 6A, using cuvettes No. 6–310 and adapter No. 6–108; (2) Hematocrit Centrifuge* (Fig. 1); (3) Heparinized capillary tubes, 75 mm. long (Aloe No. 23922).

Six tubes are filled to approximately two-thirds with blood from the infant's heel. They are then sealed at one end with a small jet flame produced by a No. 17 needle strapped to a microburner for support (Fig. 2). After centrifuging for 4 minutes at 11,000 r.p.m. the tubes are broken at the junction of the plasma and the packed cells and the plasma is blown into a small watch glass. One-tenth cubic centimeter of the plasma is recovered with a 0.1 cc. serological pipette. To plasma, add 0.9 cc. of distilled water. One-tenth cubic centimeter of the diluted plasma is transferred to each of 2 microcuvettes of the spectrophotometer. To each microcuvette add 0.5 cc. of methyl alcohol. One-tenth cubic centimeter of solution A** and 0.1 cc. of freshly prepared diazo reagent[1] are then transferred into the microcuvettes containing the blank and the reacting mixture respectively. The cuvettes are allowed to stand one-half hour. Per cent transmission is read at 540 M. Values are calculated from a standard curve prepared with the use of microcuvettes (Fig. 3).

Comment. Heparinized capillary tubes have been selected to collect the blood because they fill easily and rapidly. Also simultaneous determination of the hematocrit is possible. The overall practicability, combined with the avoidance of complications we have witnessed following venipuncture in infants and children, has established this method of collection as a standard procedure in our laboratory. This method has the additional advantage that sufficient plasma can be obtained for the determination of direct reacting as well as total bilirubin. This technique of collection also produces sufficient plasma for the microdetermination of sodium, potassium and chloride level in the plasma. These microdeterminations have proven of great value in the management of infants with electrolyte disturbances.

Summary. A method for prompt determination of the plasma total and direct reacting bilirubin level without resorting to venipuncture is described. The method used for collection of plasma can also be utilized for determination of plasma electrolytes.

*International Equipment Co., Boston, Mass.

**One gram of sulfanilic acid is dissolved in 15 cc. of concentrated HCl and diluted to one liter with distilled water.

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SUMMARIO IN INTERLINGUA

Un Simple Micromethodo pro le Determination de Bilirubina in Plasma

Es describite un methodo pro le prompte determination del nivello plasmatic de bilirubina, tanto total como etiam a reaction directe, sin recurso al technica del venipuncturas. Le procedimento usate in colliger specimens de plasma es etiam usabile in determinar le concentration plasmatic del electrolytos.

THE EFFECT OF SITOSTEROL ADMINISTRATION UPON THE SERUM CHOLESTEROL LEVEL AND LIPOPROTEIN PATTERN*

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During the past several years a large number of experimental and clinical studies have appeared which indicate that disorders in lipid metabolism may play an important role in the pathogenesis of atherosclerosis. Consequent to these studies, diets low in cholesterol and fat have been employed in man with the hope of retarding atherogenesis by reducing the concentration of blood lipids. However, the fat content of these diets must be extremely low if a significant reduction in the level of the blood cholesterol and various lipoprotein fractions is to be realized. The necessary restrictions in the choice of food are an inconvenience to even the most cooperative patients, and some patients are never able to follow a satisfactory dietary program. An easily administered preparation which could decrease the blood cholesterol level without dietary restriction would be preferable to the strict low fat regimen when a reduction in the blood lipid concentration is desired. Recent studies suggest that the administration of plant sterols may result in a decline in serum lipid concentration in the face of a full diet.

Peterson and his coworkers demonstrated that the concomitant feeding of mixed soy bean sterols would nearly completely prevent the hypercholesteremia and atherosclerosis of chickens fed a high cholesterol, high fat diet[12,13]. Pollak found a similar protection against hypercholesteremia and atherosclerosis when soy bean sterols were given to cholesterol-fed rabbits. The degree of protection afforded by the plant sterols depended upon the ratio of these sterols to cholesterol in the diet[14]. He also reported that preliminary observations indicated that the serum cholesterol of human subjects on a normal diet was decreased by the administration of a mixed soy sterol preparation containing 75 to 80% sitosterol[15]. Best's group, using a different sitosterol preparation in larger doses than those employed by Pollak, also observed a reduction in the serum cholesterol of patients on an unrestricted diet[3].

In contrast to these results, Dreisbach and his coworkers failed to demonstrate a decrease in hypercholesteremia or atherosclerosis when soy bean sterols were given to cholesterol-fed

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rabbits[5]. Likewise, Wilkinson and his group found no prolonged or marked change in the blood lipids of human subjects given a sitosterol preparation[20].

The present study of the serum cholesterol level and lipoprotein pattern of human subjects was therefore undertaken to: 1) observe the effect of sitosterol in persons on an unrestricted diet having different control serum cholesterol levels, 2) determine the response to various doses of sitosterol, 3) compare the effects of two different beta sitosterol preparations, 4) determine if the addition of sitosterol would produce further decrease in the blood lipids of persons whose serum cholesterol had been reduced by a low fat diet.

Procedure and Methods. In the first part of this work the "double blind" method was used to study the effect of sitosterol administration in 7 patients from the Cardiac Clinic of the Hospital of the University of Pennsylvania. Patients were chosen who were known to be cooperative and conscientious in following treatment. They were all consuming a full normal diet and none knew the purpose for which the sitosterol was given. There were 4 women, aged 39 to 50, and 3 men, aged 34 to 62, in the group. Five of the patients had control serum cholesterol levels below 300 per 100 cc. Four of these had mild or moderately severe essential hypertension; the other (L.S.) had pseudoxanthoma elasticum with angina pectoris and intermittent claudication. The sixth patient (A.G.) was a 39-year-old woman with a cholesterol level just over 300 mg. per 100 cc. who had previously suffered one episode of "coronary insufficiency" with substernal pain and transient electrocardiographic abnormalities persisting for 3 days. The other patient (G.) was a 41-year-old female who had rheumatic valvular heart disease, xanthelasma, and moderate essential hypercholesteremia.

The sitosterol preparation given these patients was a 13% suspension of beta sitosterol derived from tall oil. This preparation is designated Drug A in this report.*

After a 4-week control period, the drug or a placebo of similar taste and appearance was given for 4 weeks. This was followed by a 4-week course of the alternate preparation, that is, drug or placebo. The study was terminated after another 4-week control period without drug or placebo. The sitosterol dosage ranged from 6 to 15 gm. per day in the series, but was kept as constant as possible for each patient. The drug was taken in divided doses just before food. The patients were seen each week and a fasting blood specimen obtained.

Serum cholesterol was determined by the method of Abell, Levy, Brodie, and Kendall[1]. At one or 2-week intervals the serum was also subjected to filter paper electrophoresis performed at 100 volts in the horizontal, freely suspended apparatus described by Grassmann and Hannig using a barbital-sodium acetate buffer with a pH of 8.6 and ionic strength of 0.1[7]. Strips were stained for protein with amido black 10B. The protein pattern was plotted on graph paper from readings obtained from the strip using a Grassmann, Hannig, Knedel photometer[8]. Simultaneously, strips were stained for lipid with Sudan black B using the method of Swahn[18]. The lipid pattern was plotted from readings obtained directly from unclarified strips with a Photovolt densitometer.

In the second portion of this study a different sitosterol preparation was used, designated as Drug B. This drug was in the form of a powder containing 85% beta sitosterol derived from tall oil. The powder was mixed with water and taken in divided doses before meals in the same manner as Drug A. The study procedure was essentially the same as with Drug A except that no placebo was used. Following the completion of the double blind study with Drug A, Drug B was given to the 2 patients from that study (G. and A.G.) who had the highest control cholesterol values. In an attempt to determine if sitosterol might be useful in augmenting a low fat, low cholesterol diet, the powdered drug was also given to 2 patients with hypercholesteremia who had been followed for long periods while on such a diet. Both of these patients had achieved considerable reduction of blood cholesterol with diet, but they were still hypercholesteremic. These 2 patients were chosen from among several patients with hypercholesteremia who are being treated with diet. They were selected because their cholesterol

*We are indebted to Dr. Robert E. Shipley of Eli Lilly & Company for supplies of Drug A and to Dr. Mark H. Lund of the Squibb Institute for Medical Research for supplies of Drug B.

levels had fluctuated little in many months, and they were well accustomed to their diet.

Results. SERUM CHOLESTEROL LEVEL. The mean serum cholesterol levels (mg. per 100 cc.) for the 7 patients comprising the double blind test were: first control period, 278; receiving sitosterol, 247; receiving placebo, 278; last control period, 272. Table 1 summarizes the changes occurring in the serum cholesterol level during 11 courses of sitosterol administration in the 9 patients receiving either Drug A or B.

TABLE 1.—THE EFFECT OF SITOSTEROL ADMINISTRATION UPON THE MEAN SERUM CHOLESTEROL LEVEL DURING 11 COURSES OF DRUG TREATMENT IN THE 9 PATIENTS OF THIS STUDY. PATIENTS F. AND K. CONSUMED A STANDARD LOW FAT DIET DURING THE CONTROL AND TREATMENT PERIODS. ALL OTHER SUBJECTS RECEIVED AN UNRESTRICTED DIET.

Patient	*Drug*	*Gm/D*	*Mean Control*	*% Change In Mean Under Treatment*
E.S.	A	6	248±18	+ 2.4%
F.W.	A	8	229±16	− 8.7%
W.S.	A	9	272±23	− 9.8%
A.S.	A	12	243±12	−16.0%
L.S.	A	12	288±20	−16.3%
G.	A	15	365±14	−10.1%
A.G.	A	15	306±16	−11.8%
G.	B	12	360±20	−10.2%
A.G.	B	15	305±6	−17.4%
F.	B	15	388±5	−47.0%
K.	B	12–10	883±58	−24.1%

Drug: A—Suspension 13% β sitosterol
B—Powder 85% β sitosterol

The first 7 cases in Table 1, representing the double blind test, are listed in order of increasing sitosterol dosages. Although the mean level during treatment was lower than the mean control value in all patients except E.S., the difference between the means was not significant with a dose of less than 10 gm. per day. Patients E.S. and A.S. had comparable control cholesterol levels. The mean cholesterol of E.S. was slightly higher during treatment with 6 gm. sitosterol than during the control period. A.S., on the other hand, received twice as much sitosterol and his mean cholesterol level was 16% lower during treatment than during the control period. Although the absolute fall in cholesterol was generally greater in patients with higher cholesterol values, there was some variation between individuals in their response. A.S. and L.S., for example, had a greater percentage change in cholesterol than some patients with higher control values who received a slightly larger dose of the drug.

A comparison of the two preparations employed in this study is seen for Patients G. and A.G. Drug B seemed to exert a slightly greater effect upon the serum cholesterol levels of these 2 patients than did comparable doses of Drug A. Drug A, however, was more easily administered and somewhat more palatable than Drug B. The minor difference between the two preparations during the short treatment courses employed here did not appear to be of importance.

The two hypercholesteremic patients (F. and K.) on a fat restricted diet showed the greatest absolute and percentage change of any of the patients. F. is a 39-year-old male who had a cholesterol level of 700 while on a normal diet. While on a low fat diet his cholesterol for the preceding 6 months had become stabilized at about 380 mg. per 100 cc. His cholesterol level fell progressively on treatment and reached a low point of 174 mg. per 100 cc. when sitosterol was stopped at the end of the fourth week. Patient K. is a young boy who had been on a low fat diet for 4 years preceding the course of sitosterol. The cholesterol levels of this patient during the control and treatment periods are charted in Fig. 4.

The changes occurring in the serum cholesterol concentration during each of the eleven treatment periods in the 9 patients studied are also summarized in Fig. 1. In the left half of this figure the mean control cholesterol level is plotted against the respective mean treatment level for each course of sitosterol administration. The stars indicate the 2 patients on a fat restricted diet.

The effect of sitosterol administration in persons with different control cholesterol levels is illustrated in Figs. 2 to 4. Figure 2 represents the total serum cholesterol values obtained weekly in patient A.G., who has a control cholesterol level of slightly above 300 mg. per 100 cc. Both Drugs A and B were given to this patient. The progressive decline in cholesterol values

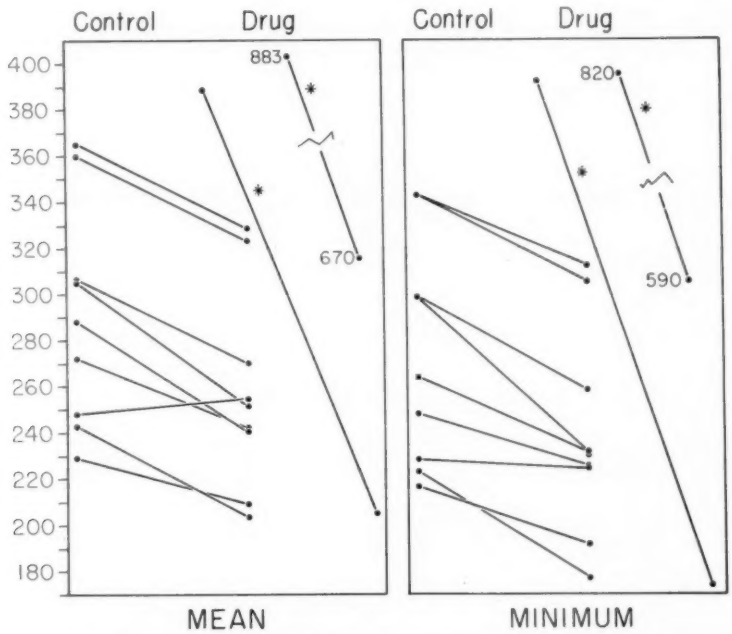

Fig. 1.—In the left half of this figure the mean control cholesterol level is plotted against the respective mean treatment level for each course of sitosterol. On the right, the lowest cholesterol value recorded during the control or placebo period is plotted against the lowest point reached during sitosterol administration. Asterisks denote 2 patients on fat restricted diets.

In some cases the cholesterol fell after the first week of therapy to a new level around which it seemed to fluctuate during the remaining 3 weeks. In others there was a gradual decline to the lowest point at the end of treatment. To the right in Fig. 1 the lowest cholesterol determination obtained at any time during the control or placebo period is plotted against the lowest value reported during therapy.

observed during the first period of treatment is repeated during the second course of drug which was extended for 5 weeks. Figure 3 reproduces the values obtained in G with a persistently elevated control cholesterol level. The placebo preparation did not affect the cholesterol level. The decrease in total serum cholesterol is again noted during both treatment periods. The rather wide fluctuations in the level after the

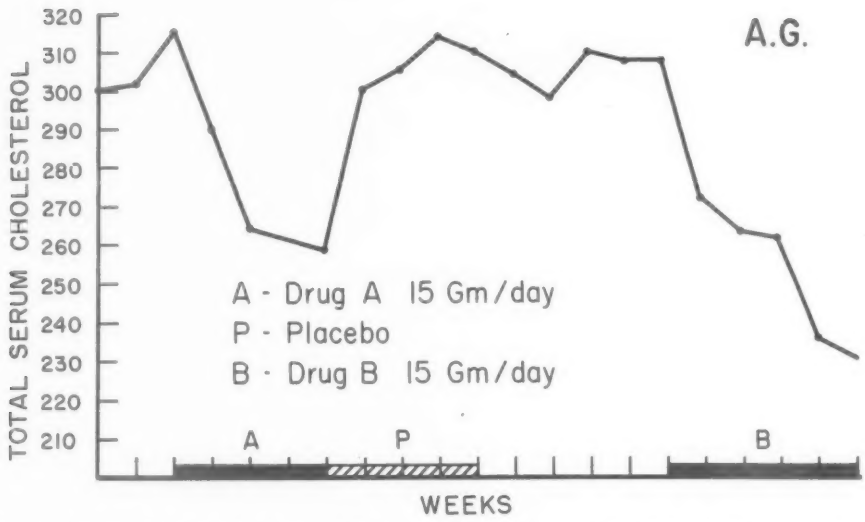

Fig. 2.—Serum cholesterol values of Patient A.G. during control, placebo and sitosterol treatment periods. The diet was unrestricted.

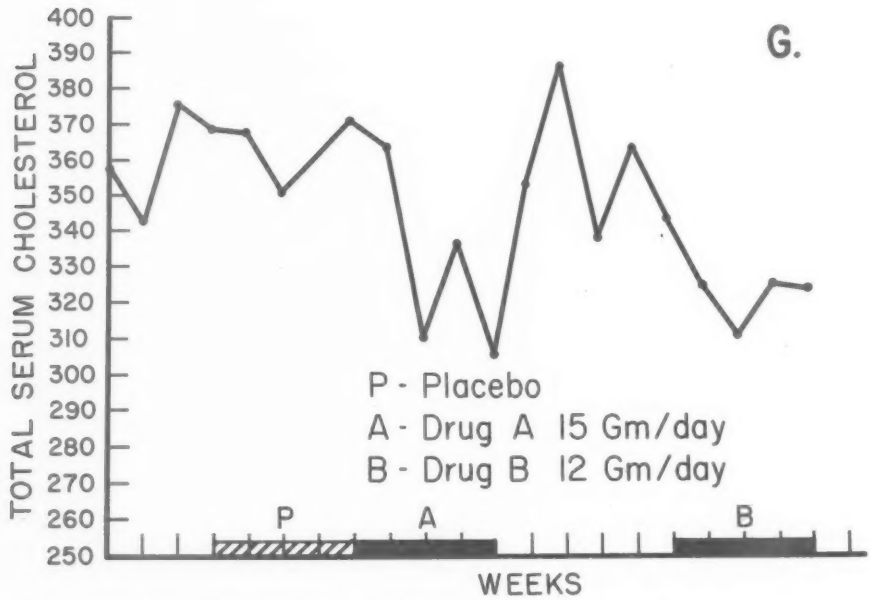

Fig. 3.—Serum cholesterol values of Patient G. during control, placebo and sitosterol treatment periods. The diet was unrestricted.

first course of treatment were noted for the first 2 or 3 weeks after the drug in about half the patients.

In Fig. 4 the serum cholesterol values are recorded for one of the patients with hypercholesteremia who consumed a standard low fat diet before and during sitosterol administration. This patient is a 7-year-old boy who developed large tendon xanthoma at the age of 3 when his serum cholesterol was 1200 mg. per 100 cc. With diet his cholesterol has been reduced but no resolution of xanthoma has occurred. The dotted line connects cholesterol values obtained at 6-week intervals for the preceding 6 months and are typical of the range and fluctuation he had exhibited for the past year. In the control period immediately preceding the drug administration, determinations were done every 2 weeks. The dosage employed in this 40-pound boy was relatively larger than those given the adults comprising the other cases in this report. Unfortunately, a prolonged period of observation while receiving sitosterol has not yet been possible.

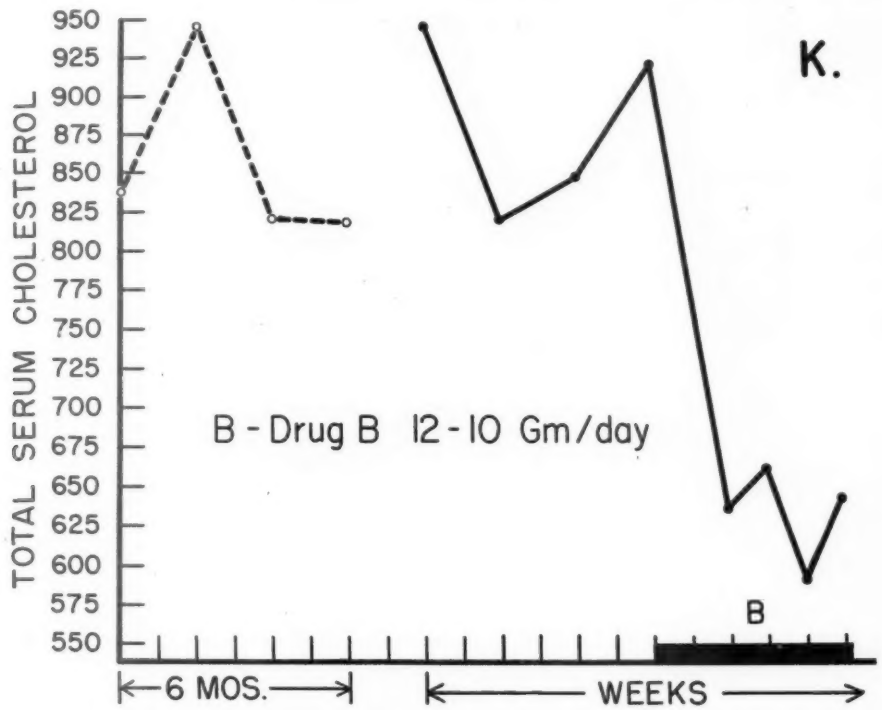

Fig. 4.—Serum cholesterol values of Patient K. during control and sitosterol treatment periods. This patient was on a low fat diet which he had followed for many years. The dotted line indicates the serum cholesterol level during the previous 6 months, and are typical of the range and fluctuation during the year preceding sitosterol administration.

ELECTROPHORETIC PATTERN. The type of alteration occurring in the electrophoretic pattern during sitosterol administration was similar in all patients. Although no quantitative correlation between the serum cholesterol level and the lipoprotein pattern was at-

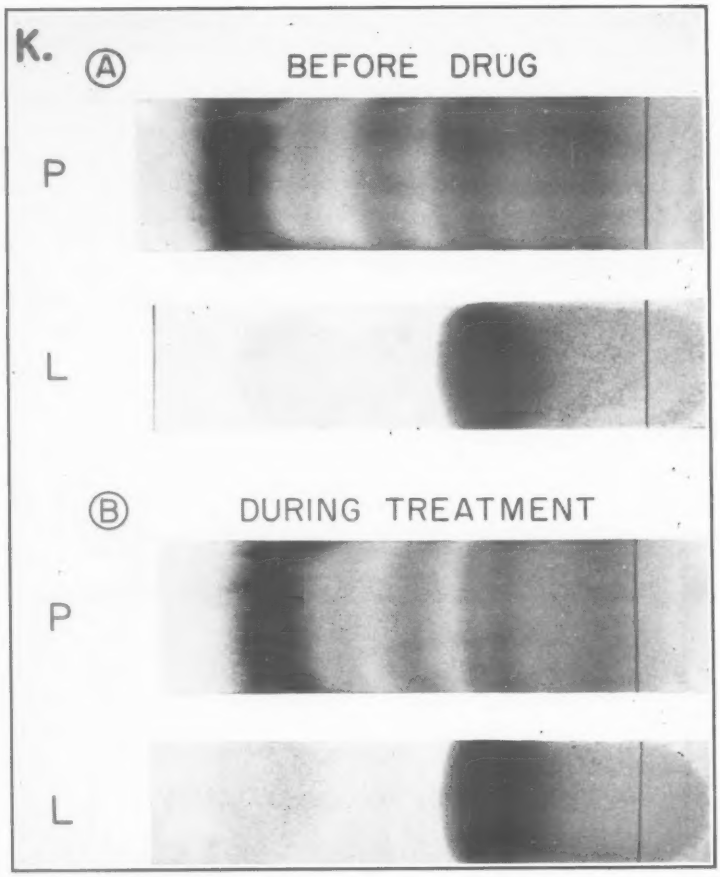

Fig. 5.—Filter paper electrophoresis strips for Patient K. obtained during the control and sitosterol treatment periods. *P*: Strip stained for protein. *L*: strip stained for lipid. Vertical dark lines on strip denote point of serum application.

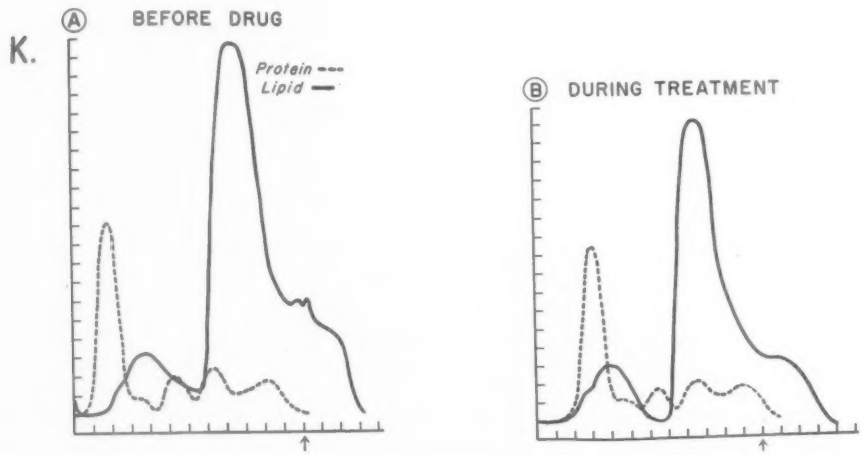

Fig. 6.—Lipid and protein electrophoretic patterns of Patient K. plotted from strips shown in Fig. 5. Control determination (*A*) was made when the serum cholesterol was 920 mg./100 cc. Treatment pattern (*B*) obtained when the cholesterol had fallen to 644 mg./100 cc. during sitosterol therapy. Arrow denotes point of application of serum.

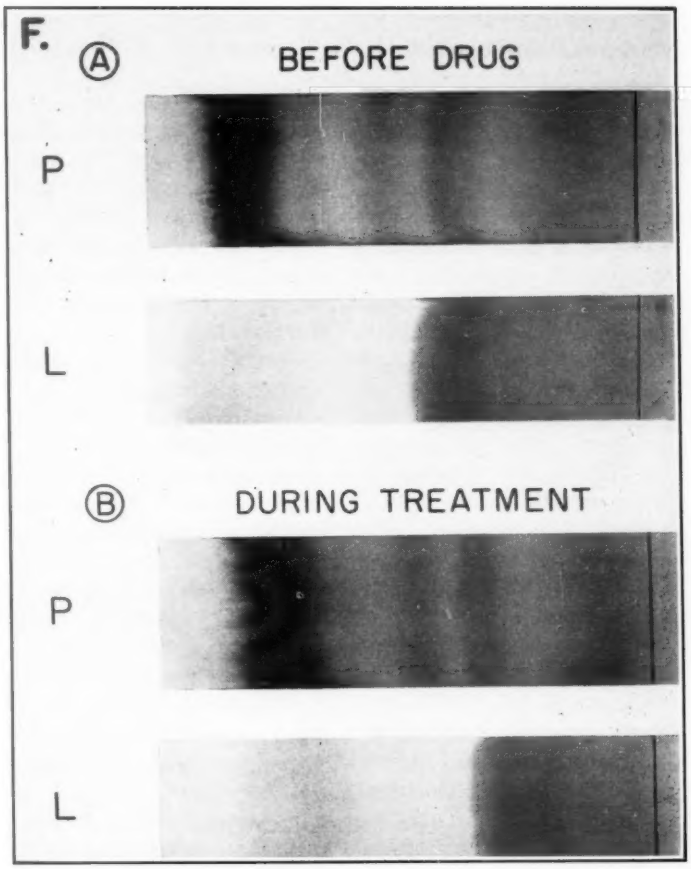

Fig. 7.—Filter paper electrophoresis strips for Patient F. obtained during the control and sitosterol treatment periods. *P*: strip stained for protein. *L*: strip stained for lipid.

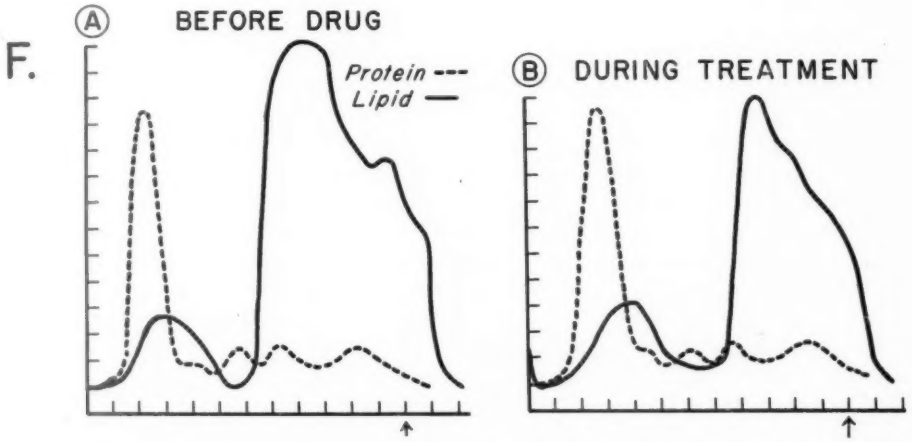

Fig. 8.—Lipid and protein electrophoretic patterns of Patient F. plotted from strips shown in Fig. 7. Control determination (*A*) was made when the serum cholesterol was 397 mg./100 cc. Treatment pattern (*B*) obtained when cholesterol had fallen to 199 mg./100 cc. The control and treatment lipid patterns differ from that of the other patients in showing an unusually prominent "hump" near the point of application (denoted by arrow).

tempted, the changes in the pattern became more striking with greater changes in the cholesterol concentration. When there was little or no change in the cholesterol level, there was no apparent alteration in the electrophoretogram. Examples of the electrophoretic patterns obtained with more marked reduction in the serum cholesterol level are illustrated in Figs. 5 through 8.

Paper strips stained for protein and fat using the serum of Patient K are reproduced in Fig. 5, and the corresponding patterns are plotted in Fig. 6. The vertical dark lines in the strips and the arrows beneath the graphs denote the point of application of serum. The control determination (Figs. 5A and 6A) was made when the serum cholesterol was 920 mg. per 100 cc. The treatment pattern (Figs. 5B and 6B is from serum drawn 3 weeks later when the cholesterol level had fallen to 644 mg. per 100 cc. during sitosterol administration. In this patient, as in all others, no significant alteration in the protein pattern was detected during the study. The type of change occurring in the lipid pattern is typical of that seen in all cases when the serum cholesterol was significantly reduced. The lipid stained in the region corresponding to the albumin, alpha-1 globulin zone appears similar in the control and treatment serum. In contrast, the height and area of the lipid zone extending from the region of the beta globulin to the cathode side of the point of application is markedly reduced following sitosterol administration.

The control pattern in Figs. 7 and 8 was obtained when Patient F had a total serum cholesterol concentration of 397 mg. per 100 cc. The treatment specimen was drawn 3 weeks after the control. In the interim he had received sitosterol and the total cholesterol had fallen to 199 mg. per 100 cc. The protein pattern is not significantly altered during treatment. Comparison of the lipid strips again shows that the alpha fraction appears similiar in both specimens; whereas the lipid staining in the beta globulin region and near the point of application is decreased during treatment.

During this study, and for over a year preceding this period, the patient was on a well controlled 20 to 30 gm. fat diet. Before dietary therapy his fasting serum was persistently milky in appearance. With a low fat diet the fasting serum was much clearer but remained slightly lactescent. Clinical observations done at other times have shown that his blood neutral fat concentration is elevated even when he is consuming the strict low fat diet. The electrophoretograms of this patient differ from those of the other subjects in the study in that both the control and treatment patterns show an unusual prominence of the lipid zone which is indistinctly separated from the beta peak and extends to the cathode side of the point of application. The increased size of this "hump" is probably related to the elevated blood neutral fat level. Kunkel and Slater reported that the neutral fat content of this zone was higher than that of the main beta peak[10]. Swahn found nearly all of the serum neutral fat located near the point of application and in the tall beta component. The greatest concentration was in the fraction nearest the starting point, with a lesser peak in the tall beta zone. Only negligible amounts were found in alpha lipid[18]. However, this lipid zone behind the beta peak does not consist only of neutral fat. Kunkel and Slater found the ratio of cholesterol to phospholipid in this zone to be essentially the same as in the beta globulin region[10]. Although this zone is prominent in both the con-

trol and treatment patterns of Patient F, the decrease in this component along with the main beta peak during treatment is similar to the response seen in all patients.

Discussion. During these observations none of the patients exhibited more than normal minimal weight fluctuations. No upset in usual bowel habits was reported and no untoward side effects were noted. The liquid preparation was somewhat more palatable than the powdered material, but none of the patients objected to either form of the drug.

The results of this study indicate that the serum cholesterol level can be reduced by sitosterol administration while the diet is unrestricted and body weight remains stable. This was true regardless of the initial cholesterol concentration. Neither the optimum dose nor the maximum tolerated dose can be determined from this series. The minimum effective dose seems to be above 10 gm. a day. These results, of course, apply to the stort course of drug treatment employed in this study. With prolonged treatment, it is possible that resistance to the drug might develop or some undesirable side effects become apparent. On the other hand, a smaller dose than that used in this study might be effective if continued for a longer period.

In the 2 patients who apparently had achieved as great a reduction in serum cholesterol as was possible with a low fat diet practical for long term use, the addition of sitosterol effected a further decrease in serum lipid. These 2 patients showed the greatest decrease in serum cholesterol observed in the study. If sitosterol acts by preventing the normal intestinal absorption of exogenous lipid and resorption of endogenous lipid, the greater response of these 2 patients was probably due to their receiving more sitosterol in proportion to fat in the diet than did the other subjects. However, the mechanism of action of sitosterol is not definitely known.

Hernandez and coworkers reported that the concomitant feeding of sitosterol with labeled cholesterol greatly decreased the total amount of cholesterol which could be recovered from the thoracic duct of rats and decreased the percentage of thoracic duct cholesterol which was in ester form[9]. This suggested that sitosterol may hinder cholesterol absorption by retarding esterification. Swell and his group found that sitosterol could be esterified in an *in vitro* system with pancreatic cholesterol esterase, oleic acid, and bile salt[19]. The reaction proceeded somewhat slower than cholesterol esterification. Rosenman, Byers and Friedman, however, failed to demonstrate a decrease in thoracic duct cholesterol when sitosterol was combined with cholesterol feeding in rats[17]. Pollak suggested that sitosterol might prevent cholesterol absorption by the formation of a nonabsorbable cholesterol-sitosterol complex since he obtained a single crystal from an alcohol-acetone mixture of the two substances[14]. Apparently sitosterol itself is not completely rejected by the gastrointestinal tract. Gould's recent studies using radioisotope labeled sterols showed that sitosterol was absorbed. However the absorption was not nearly as complete as cholesterol absorption, and sitosterol disappeared from the blood much faster than cholesterol[6]. Although sitosterol may act entirely by retarding the intestinal absorption of cholesterol, the possibility of some other mechanism has not been excluded.

The changes in the electrophoretic pattern which occurred with significant reduction in the serum cholesterol were similar in all patients. While the

proteins and the alpha lipid compoment were unchanged by sitosterol ingestion, there was a decrease in the larger lipid zone encompassing the tall beta spike and extending behind the point of application. The decrease in serum cholesterol during treatment represents a loss from this fraction. However, the change in the electrophoretic pattern may not be due entirely to a decrease in cholesterol. There appeared to be a comparable decrease in the tall beta peak with its high cholesterol concentration and the beta area nearer the point of application which supposedly has a high neutral fat content and a lesser amount of cholesterol. Preliminary studies by Best's group indicate that serum neutral fat as well as cholesterol may be reduced by sitosterol ingestion[3]. The changes in the electrophoretic pattern are consistent with a decrease in other lipid in addition to cholesterol.

Several workers have found that atherosclerotic patients tend to have higher lipid in the beta fraction than do normals. The absolute and relative amount of cholesterol in the beta fraction separated by filter paper electrophoresis was found by Nikkilä to be generally higher in atherosclerotic subjects than in supposedly normal persons[11]. Rosenberg, also using paper electrophoresis, found a greater proportion of lipid in the large beta zone in atherosclerotic than in normal subjects[16]. Earlier, Barr's group employed Cohn's chemical method of protein fractionation to study the distribution of cholesterol between the alpha and beta lipoprotein fractions[2,4]. They found that survivors of myocardial infarction and patients having conditions predisposing to atherosclerosis tended to have a greater percentage of total cholesterol in the beta containing fraction than did supposedly normal young subjects. Despite the differences in methods, there appears to be rather good agreement between the fractions separated by the chemical method and by the paper electrophoresis technique[10,11,18]. In all of these studies on groups of patients there has been considerable overlap with some apparently normal persons having values more "abnormal" than some patients with known atherosclerosis. Contrariwise, the results in some atherosclerotic subjects fell within the range of the "normal." Nevertheless, these studies do indicate a general tendency for increased lipid in the beta fraction in atherosclerotic patients. During sitosterol administration the lipid in this beta fraction decreased. As yet, however, there is no direct evidence that decreasing the beta lipid in man will retard or prevent atherosclerosis. The hope that atherogenesis may be retarded by correcting lipid abnormalities appears justified by the continuing accumulation of experimental and clinical data indicating an increase in atherosclerosis in the presence of hypercholesteremia and lipoprotein abnormalities. The low fat diet, while effective in reducing the serum cholesterol, is an inconvenience and sometimes difficult to enforce over long periods. When a reduction in serum cholesterol is desired, sitosterol administration offers the possibility of accomplishing this without dietary restriction.

Summary. 1. Beta sitosterol administration produced a reduction in the serum cholesterol concentration of patients on an unrestricted diet regardless of their initial cholesterol level. No untoward side effects were noted and none of the subjects had a significant change in weight.

2. The minimum effective dose of sitosterol for a 4-week course of treatment was above 10 gm. a day. The maximum tolerated dose was not determined.

3. In 2 patients on a strict low fat diet, the addition of sitosterol produced a further lowering of the serum cholesterol.

4. With significant reduction in the cholesterol concentration, certain changes were demonstrable in the electrophoretic lipoprotein pattern. When compared with control patterns, treatment patterns revealed:

a. A decrease in the large beta lipid zone, including the tall beta peak and extending to the cathode side of the point of application.

b. No significant change in the alpha lipid fraction or in the protein pattern.

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(Interlingua on page 674)

SIMULTANEOUS DETERMINATION OF CARDIOVASCULAR-RENAL FUNCTIONS IN MAN BY A CONSTANT INFUSION TECHNIQUE*

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We have described elsewhere[9] a method for the determination of the cardiac output in the human subject by a direct Fick procedure employing infusions of para-aminohippuric (PAH) acid. In essence, this method consists of the continuous infusion of PAH from a constant infusion pump. The mixed venous concentration of PAH is determined by discontinuing the infusion suddenly and extrapolating the arterial disappearance curve to the moment of discontinuation. The arterial PAH concentration is the observed arterial concentration at the same moment. The numerator of the Fick equation is simply the rate of PAH infusion.

The method has the technical advantages of eliminating the need for cardiac catheterization, all required information being obtained by analysis of arterial samples, and of further substituting the blood analysis for the more tedious gas procedures. It has the further advantage that the same data used in the calculation of cardiac output may also be employed in the estimation of the plasma clearance of PAH and the volume of distribution of PAH. Thus the important circulatory parameters of cardiac output, renal plasma flow and fluid volumes are estimated simultaneously in one procedure.

Although PAH is especially suitable for this determination because of its high plasma clearance (which makes the difference between the terms of the denominator of the Fick equation usably large) the same principles may be applied to any other substance whose plasma clearance is independent of its concentration (that is, volume-limited). The present report describes the estimation of the mannitol clearance and the volume of distribution of mannitol in human subjects by precisely the same technique previously

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employed with PAH. These measurements were made simultaneously with measurements of PAH clearance and distribution volume. It was also found possible, with a minimum of further manipulation, to estimate the blood volume and total body water in these subjects and to secure a validating estimate of cardiac output by the dye dilution technique[6] employing Evans blue.

It will be shown below that the following measurements can be made on human subjects from the analysis of 11 arterial blood samples: blood volume, mannitol space, PAH space, total body water, cardiac output, plasma mannitol clearance and plasma PAH clearance. Neither cardiac nor bladder catheterization is required and no gas analyses are necessary. The technique has yielded satisfactory results in our hands according to criteria presented below in over 50 sets of determinations carried out on volunteers and on patients admitted to the Obstetrics and Gynecology Service at the Ohio State University Medical Center. Of all subjects used in this study, a total of 10 were nonpregnant and form the basis of the present report.

Principles. ESTIMATION OF CLEARANCES. Clearances of PAH and mannitol determined by this method are estimated from the ratio between the infusion rate and the equilibrium concentration attained at the end of the infusion. The clearance so determined is, of course, the plasma clearance. In the case of mannitol, this value may be somewhat higher than the glomerular filtration rate due to mannitol metabolism[4] although the extent of this is probably small, and has been reported to be zero[2,5]. In the case of PAH, the clearance may be somewhat larger than the actual renal plasma flow owing to acetylation of PAH unless the plasma PAH is determined on hydrolyzed samples[13].

DETERMINATION OF VOLUMES OF DISTRIBUTION. The volumes of distribution are estimated by the infusion slope method of Schwartz[11]. The slope of the disappearance curve after the infusion has been discontinued is the ratio between the clearance and the volume of distribution. Since the clearance is known from the ratio of the infusion rate to the equilibrium concentration, the volume of distribution is readily calculated.

THE REQUIREMENT OF CONCENTRATION EQUILIBRIUM. Occasionally concentration equilibrium is not achieved despite the use of a primer and a 35-minute infusion. We have shown elsewhere[9] (equations 4 and 5) that despite the failure of concentration equilibrium, the calculation of clearance and volume of distribution can still be made. The calculations are somewhat tedious, and are rarely necessary. Plasma concentration equilibrium within the limits of analytical accuracy was attained in all the experiments reported here.

ESTIMATION OF BLOOD VOLUME AND TOTAL BODY WATER. The plasma volume was estimated from the Evans blue space at 10 minutes. This was converted to blood volume by multiplying by (1/1-Hct). The total body water was estimated from the antipyrine space at zero time, obtained by extrapolating the antipyrine concentrations at 2 and 3 hours to this time, and dividing the injected dose of antipyrine by its virtual concentration at zero time[1].

DYE DILUTION ESTIMATE OF CARDIAC OUTPUT. The Evans blue employed in the estimation of blood volume served also to yield a value for the cardiac output, the dye dilution curve being prepared from samples collected at two-second intervals for one minute just after the injection of the dye. The

curves were analyzed by the method of Hamilton and Remington[6].

THE CHOICE OF PRIMING DOSES. Concentration equilibrium is attained most rapidly when the primer is so chosen as to approximate concentration equilibrium at once. This may be achieved simply by making the ratio of priming dose to minute infusion rate the same as the ratio of anticipated volume of distribution to the minute clearance. In the case of PAH this was attempted by making the primer thirty-two times the infusion rate; in the case of mannitol, the primer was fifty times the infusion rate. (These figures were set up as standards before the present experiments were completed. In the light of our present knowledge, they should be revised so that the PAH primer is twenty times the minute infusion rate and the mannitol primer 100 times the minute infusion rate.)

THE CRITERION OF VALIDITY OF THE SPACE AND CLEARANCE MEASUREMENTS. In our original work with PAH[9] we showed that the cardiac output measurement by the "stopped infusion" technique was critically dependent on the accuracy of the construction of the disappearance curve. Only when the disappearance curve is accurately constructed is it possible to obtain an accurate cardiac output estimate. However, since the disappearance curve is certain to present an anomalous appearance and slope when mixing is defective, such defective mixing must necessarily result in the appearance of an erroneous cardiac output. Contrariwise, it may be stated that when the cardiac output is correctly estimated from the "stopped infusion" method, the disappearance curve has been properly constructed, and the data derived from it are valid. We have rarely observed discrepancies between the cardiac output estimated by the dye dilution method and the "stopped infusion" method; in most cases these have been associated with visible edema. In the present series we have not employed any data from experiments in which the two methods for determination of the cardiac output failed to agree within 25%.

Methods. CLINICAL. The patients were either already hospital in-patients, or else were admitted to the hospital the evening before the test: all were in good general physical condition. Bed rest continued throughout the testing period. Breakfast was withheld, but water was allowed *ad lib.* prior to the beginning of the infusion.

A sample protocol is shown in Table 1. Antipyrine 1.0 gm. was administered intravenously at 7:00 A.M. Two hours later, following the introduction of a Cournand-type arterial needle, a blood sample was taken and a "priming dose" consisting of 35 cc. of 25% mannitol and 5 cc. of 20% para-aminohippuric acid was given. Immediately upon completion of the priming dose, there was begun the constant infusion of a solution of 20% mannitol and 4% para-aminohippuric acid, at the rate of 0.8 cc./minute through a constant infusion pump. This infusion was continued for 35 minutes, and brachial arterial blood samples were taken at 20, 25, 30 and 35 minutes. The infusion was then discontinued and arterial blood samples were taken at 2, 4, 6, and 8 minutes. After the 8-minute specimen, 25 mg. of T–1824 were injected rapidly, and arterial blood samples collected at 2-second intervals for 60 seconds in a sample collector driven by the infusion pump[8]. A subsequent arterial sample was taken 10 minutes later, and the arterial needle was withdrawn.

CHEMICAL. *Determination of Evans Blue.* The determination of Evans blue for the blood volume estimation was made in the following manner: An aliquot of the plasma from blood sample No. 11 was diluted with 2 volumes of saline and the optical density read against a blank plasma similarly diluted in the Beckman DU spectrophotometer at 620 mu. The standard for this determination was made from 10 gammas of Evans blue diluted in 1 cc. of saline. To this were added one volume of saline and 1 cc. of the patient's blank plasma. This served to correct for the variable color change produced by plasma on Evans blue.

In the estimation of cardiac output, the

samples from the sample collector were too small to permit of centrifugation of the plasma. They were consequently handled in the following manner. Whole blood was pipetted, after stirring, 0.2 cc. ordinarily being taken. The blood was diluted with 2.8 cc. of isotonic saline and the cells centrifuged. The supernatant was read against a blank whole blood sample similarly treated. The standard was made by pipetting 0.2 cc. of Evans blue containing 2 gammas into 2.6 cc. of saline, and adding to this 0.2 cc. of whole blank blood. The cardiac outputs obtained when whole blood was pipetted in the manner described are cardiac output of whole blood and no hematocrit correction is required.

Results. The results in 10 essentially normal subjects are given in Table 2. Particular attention is directed to the following:

The cardiac outputs in these subjects as determined by the dye dilution method and the "stopped infusion" method agreed in every case within 25%. The averages obtained by the two methods agreed within 1.5%. The average values of 7.54 and 7.44 L. per minute were somewhat higher than is usually considered normal for subjects

TABLE 1.—SAMPLE PROTOCOL

NAME: DATE:

Time (min.)	*Actual Time*	*Procedure*	*Sample (blood/cc.)*	
...		1. Antipyrine blank	(1)	5
0		2. Inject antipyrine 1.0 gm. (1 ampule)*		
115		3. Mannitol, PAH, Evans blue blank, Antipyrine No. 1	(2)	10
117		4. Primer: 35 cc. of 25% Mannitol and 5 cc. of 20% PAH		
120		5. Infusion: 0.8 cc./min. 20% Mannitol, 4% PAH		
140		6. Samples during infusion	(3)	10
145		7. Samples during infusion	(4)	10
150		8. Samples during infusion	(5)	10
155		9. Discontinue infusion	(6)	10
157		10. Samples after infusion	(7)	10
159		11. Samples after infusion	(8)	10
161		12. Samples after infusion	(9)	10
163		13. Samples after infusion	(10)	10
165		14. Inject 1 ampule Evans blue rapidly; run sample collector 60 sec.		
175		15. Evans blue Sample Antipyrine No. 2	(11)	10

* The antipyrine used in this study was generously supplied by Eli Lilly and Company.

Determination of mannitol, PAH, and antipyrine. Antipyrine determinations were made on samples 1, 2 and 11. PAH and mannitol were determined on samples 2 to 11. The analyses were all made on plasma deproteinized with cadmium hydroxide. The results in the case of antipyrine with the cadmium hydroxide precipitation were found to be identical with those obtained when the recommended zinc hydroxide precipitation is employed.

Mannitol was determined by the method of Corcoran and Page[3]; PAH by the method of Smith *et al.*[12]. Antipyrine was measured by the method of Brodie[1].

All color readings were made on the Beckman DU spectrophotometer.

of the size and body build employed. The cardiac index was 4.01 L./M^2, compared to the accepted value of 3.0 to 3.5 L./M^2.

The volume of distribution of PAH averaged 14.5% of the body weight, compared to the volume of distribution of mannitol of 16.4% of the body weight. The variability in any comparison was, however, too great to permit of the statement that there was any systematic difference between the two values.

TABLE 2.—CARDIAC OUTPUTS, BODY FLUID SPACES, AND RENAL CLEARANCES IN 10 NORMAL SUBJECTS DETERMINED BY THE METHODS DESCRIBED IN THE TEXT

		Male or Female	*Weight (kg.)*	*Height (cm.)*	*Body Surface (M²)*	*Spaces (% body weight)*			*Clearances (cc./min.)*		*Filtration Fraction MA/PAH*	*Cardiac Output (L./min.)*		*Cardiac Output Index (L./min./M²)*	
						PAH	*MA*	*AP*	*EB*	*PAH*	*MA*		*EB*	*PAH*	*EB*	*PAH*
1. R. B.	Healthy physician	M	92.4	186	2.17	13.5	18.0	69.9	7.6	622	95	.153	7.9	6.86	3.64	3.16
2. W. M.	Healthy physician	M	75.1	186	2.00	15.6	12.2	49.0	7.9	750	139	.185	6.05	5.47	3.03	2.74
3. M. M.	Healthy med. student	M	63.1	173	1.76	17.3	18.0	..	8.3	744	151	.203	7.83	7.18	4.45	4.08
4. L. S.	Mild P.I.D.	F	82.0	160	1.85	12.9	15.1	..	6.0	671	162	.241	8.37	10.2	4.52	5.51
5. I. H.	Healthy med. student	M	72.7	178	1.90	10.6	13.8	62.5	7.7	423	105	.248	8.8	8.5	4.63	4.48
6. C. H.	Healthy physician	M	86.1	183	2.08	10.1	14.6	65.0	7.0	462	131	.284	11.83	12.0	5.70	6.20
7. M. Ha.	Healthy physician	M	80.0	185	2.04	9.74	16.3	62.5	7.6	564	136	.241	10.74	9.44	5.27	4.58
8. D. B.	Diag. D. & C. Healthy female	F	61.7	162	1.66	21.4	18.5	46.7	7.9	936	149	.159	4.84	4.14	2.92	2.50
9. M. Ho.	Diag. D. & C.	F	42.7	162	1.42	16.8	20.7	57.5	4.3	536	102	.190	4.06	4.15	2.86	2.92
10. C. S.	Healthy nurse	M	52.3	158	1.52	18.0	16.3	69.5	7.0	622	147	.236	4.93	5.56	3.24	3.65
	Average					14.5	16.4	60.3	7.13	633	132	.214	7.54	7.44	4.03	3.98

The antipyrine space was extraordinarily large, averaging 60.3% of the body weight, and ranging in value from 49% to 69.9% of body weight. All of the subjects were in good nutritional status, and the higher values appear improbable. This will be considered further in the discussion.

The Evans blue space averaged 7.13% of the body weight and ranged from 4.3 to 8.3% of the body weight. This value is slightly smaller than the usual figure quoted for man of 7.8% of the body weight.

The plasma clearance of PAH was 633 cc./min. on the average; the plasma clearance of mannitol was 132 cc./min. The filtration fraction ranged from .153 to .284 with an average of .214. It should be noted that the conditions of the clearance measurement were not identical with the usual ones for the measurement of bladder clearance; the patients were not prehydrated, since there was no need for urine collection.

Discussion. Although the present series of determinations is too small to permit of definitive conclusions regarding the values of the measured quantities in the normal human subject, it is presented at this time to indicate the simplicity and applicability of the techniques. It is necessary, however, to bear constantly in mind certain limitations of the procedure.

1. CARDIAC OUTPUT BY THE "STOPPED INFUSION" METHOD. The accurate determination of cardiac output by "stopped infusion" requires that the concentration of PAH in the mixed venous blood at the moment of discontinuing the infusion be carried to the arterial side of the circulation. Since some mixing will necessarily occur in transit through the heart and lungs, it is clear that no single arterial sample will accurately depict the state of the mixed venous blood at this time. On the other hand, when the disappearance of PAH is a

single exponential function of time as indicated by linearity of the disappearance curve on semilog paper, it is justified to assume that the mixed venous blood *uncontaminated by the infusion* can be described by extrapolation of the disappearance curve to the moment of discontinuing the infusion. Any deviations from linearity revealed in early blood samples represent simply the "smearing" of the last traces of the infusion in their transit through the circulation. On the other hand, if circulation is sluggish, this "smearing" may be visible for some time after the infusion is discontinued, and the linearity of the disappearance curve will be destroyed. We have not encountered this situation in any determination, but it is an important limitation of the method to remember.

A more serious limitation of the method is concerned with the homogeneity of the volume of distribution of the measuring substance. If the measuring substance has a compound volume of distribution, it will be cleared from the volume (plasma) which is in contact with the clearing organ more rapidly than from its entire volume of distribution. The disappearance curve will then be initially too steep (representing clearance from a small volume) and later too shallow (representing return to the plasma of material in the extravascular fluid). In such a case, the construction of the disappearance curve as a straight line will be impossible; attempts to fit a straight line to the data will force erroneous results in the output measurement, and the apparent volume of distribution. A mathematical analysis of such curves is possible, and has been reported elsewhere for the case of a single injection of a substance[10]. Since this situation is of infrequent occurrence, the analysis of nonlinear disappearance after a stopped infusion will not be considered here.

A further limitation on this method arises from the fact that the arteriovenous difference owes its existence to the clearance of the substance employed for the measurement. Thus with PAH, at equilibrium conditions the renal fraction of the cardiac output is given by the ratio $(A-A')/A$ where A is the concentration in the arterial blood just before stopping the infusion and A′ the extrapolated concentration at the moment of discontinuation. Clearly, if the renal fraction of the cardiac output is very small, the value of the difference $(A-A')$ will be small relative to the value of A, and the results may be prejudiced by inaccuracies in the determination of small concentration differences.

In normal subjects, none of these considerations is of significance; the application of this method to patients with cardiovascular or renal abnormality should be carried out only when these limitations are fully appreciated, and when the criterion of validity previously suggested[9] is applied.

2. PLASMA VERSUS EXCRETORY CLEARANCE. The clearances measured are plasma clearance, and describe the rate at which the material is eliminated by all routes from the plasma. They will, consequently, exceed the bladder clearance by the extent to which extrarenal elimination or metabolism exists. In the case of PAH, acetylation represents such an extrarenal removal; in the case of mannitol, metabolism may engender such an error. However, it appears unlikely to us that either error will be of major significance, (see also **Principles**).

In addition to metabolism and extrarenal removal, the plasma clearance will exceed the bladder clearance by an amount best described as a function of the inhomogeneity of the volume of

distribution. For example, mannitol may gradually penetrate an increasing volume of distribution, even while plasma concentration is maintained at equilibrium. That is to say, some of the mannitol which is entering the body is not, in fact, being eliminated, but only diluted. To equate the rate of administration under these circumstances with the rate of removal will obviously result in falsely high values for the excretory clearance.

This situation presents an important limitation on the use of such substances as inulin (which penetrates the extravascular fluids slowly) and creatinine (which penetrates intracellular fluids slowly) in this type of measurement.

Fortunately, however, the existence of significant inhomogeneity in the distribution volume is immediately indicated by application of the same criterion which is used for determination of the cardiac output. If the disappearance curve after discontinuing the infusion is straight, inhomogeneity can be assumed to be of negligible magnitude. One may be assured that the disappearance curve is in fact straight, rather than representing a loose fit of a straight line to curvilinear data, if the cardiac output estimation from the "stopped infusion" curves coincides with that obtained independently by the dye dilution method.

The basic criterion then which establishes the validity of the measurements made by this method is the coincidence of the cardiac output determined by this method with that obtained by an independent one. The cardiac output estimate by the "stopped infusion" method must depend on the construction of a satisfactory linear disappearance curve. If alinearity exists, the results must be considered with skepticism, even when the apparent cardiac output affords a satisfactory check with an independent method.

In our present series of 10 patients, this criterion was met, and our confidence in our results is thus re-enforced.

3. INFUSION-SLOPE MEASUREMENTS OF FLUID VOLUMES. For the measurement of fluid volumes by the infusion-slope method, the basic requirement for the determination is again the linearity of the disappearance curve. It may be noted that potential inaccuracies in the equation of plasma and excretory clearances are without effect on the estimation of fluid volume, since only plasma clearance is required for the volume calculation[11]. Since linear disappearance was regularly obtained in this series, the volume measurements may be considered valid.

As we have noted, the cardiac outputs which we have obtained (by both methods) are somewhat higher than those generally accepted. This may in part be due to the fact that most of the subjects were members of the hospital staff, who were young and presumably in good physical condition, but were somewhat apprehensive about the application of a new technique, although they showed no visible emotional disturbance.

The volumes of distribution of PAH and mannitol showed good agreement on the average, though occasional individual comparisons were quite poor. It is nevertheless of interest that the PAH space only exceeded the mannitol space by more than 20% in one case. This suggests that PAH is confined to the extracellular compartment in man. In the dog, the PAH space is somewhat larger than the mannitol space, but it will be recalled that corpuscular penetration by PAH occurs in the former species to an appreciable extent[7], while PAH is excluded from the red blood cell of man. This raises the interesting possibility that PAH may

be a more suitable substance than mannitol, inulin, thiosulphate, and others, for determinations of extracellular fluid volume. The ease and accuracy of its determination coupled with its rapid penetration of its final volume of distribution recommend it for this purpose.

The antipyrine space in the subjects studied (and in a subsequent series not reported here) was much larger than would have been anticipated from the nutritional status and body build of the subjects. We have no satisfactory explanation for the high values obtained at the present time, but we are inclined to suspect that antipyrine may be distributed more inhomogeneously through tissues than has been indicated previously. It may also be noted that the zero extrapolation was made on the basis of a two point disappearance curve rather than the recommended three.

Although reasonable values were obtained for mannitol clearance, the values for the PAH clearance were somewhat lower than we would have expected. In general, it appeared that the PAH clearance deviated the most from the expected value in those subjects in whom the cardiac output showed the largest upward deviations. Whether this represents a total circulatory adjustment to the anxiety provoked by the procedure remains to be determined.

Summary and Conclusions. During an infusion of PAH and mannitol which is suddenly discontinued, plasma concentration rises to an equilibrium, falls discontinuously, and then declines in an exponential manner with time.

The equilibrium concentration reached by these substances may be used for the estimation of plasma clearance; the discontinuity at the moment of stopping the infusion measures the cardiac output; the slope of the further disappearance curve measures the volume of distribution.

By combining this infusion procedure with the administration of antipyrine and Evans blue in the manner described in the text, it is possible to make simultaneous measurements of cardiac output, renal plasma flow (as PAH clearance), glomerular filtration rate (as mannitol clearance), blood volume, extracellular fluid volume (as mannitol space) and total body water. The procedure avoids the use of catheters and gas analysis. It may be repeated as often as required, and patient cooperation is necessary for only a 3-hour period for each determination.

The criteria for validity are presented and discussed and possible erors of the method are considered.

Results in a series of 10 patients indicate that reasonable values are obtained for the quantities investigated. The cardiac outputs are somewhat higher than anticipated, the total body water is likewise somewhat high. The renal plasma flow is a little lower than the figures given for normal man.

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SUMMARIO E CONCLUSIONES IN INTERLINGUA

Determination Simultanee del Functiones Cardiovascular e Renal in Humanos per Medio de un Technica a Infusion Constante

Quando le infusion de acido para-aminohippuric e de mannitol es subitemente interrumpite, le concentration plasmatic ascende verso un nivello de equilibrio, descende discontinuemente, e alora continua su descendita exponentialmente con le tempore.

Le concentration equilibrial que es attingite per iste substantias pote esser usate pro estimar le clearance plasmatic; le discontinuitate al momento del cessation del infusion mesura le rendimento cardiac; le subsequente declino del curva de disparition mesura le volumine de distribution.

Per combinar iste procedimento infusional con le administration de antipyrina e blau de Evans (in le maniera describite in le texto), il deveni possibile facer mesurationes simultanee del rendimento cardiac, del fluxo renal de plasma (como clearance de acido para-aminohippuric), del filtration glomerular (como clearance de mannitol), del volumine sanguinee, del volumine de fluido extracellular (como spatio de mannitol), e del volumine total de aqua corporee. Iste technica evita le uso de catheteres e le analyse de gas. Illo pote esser repetite tanto frequentemente como requirite, e le cooperation del patiente es necessari pro solmente un periodo de 3 horas pro cata determination.

Es presentate e discutite le criterios del validitate del methodo. Su possibile errores es considerate.

Le resultatos obtenite in un serie de 10 patientes indica que le resultatos pro le entitates investigate es toto plausibile. Le valores del rendimento cardiac es alique plus alte que expectate; etiam le valores pro le volumine total de aqua corporee es alique nimis alte. Le fluxo renal de plasma es alique plus basse que le valores citate pro humanos normal.

LOCAL CUTANEOUS RESPONSE OF NICOTINIC ACID AND ESTERS AS DIAGNOSTIC AID FOR RHEUMATOID ARTHRITIS

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Following Nassim and Banner's report[1] that 5 patients with rheumatoid arthritis had an atypical skin response to the application of tetrahydrofurfuryl ester of nicotinic acid, Streitfeld and Saslaw[3] utilized this phenomena for the evaluation of rheumatic fever activity. Since there was an apparently high correlation between rheumatic activity and lack of erythema upon local application of the drug, the possibility arose that a similar correlation might exist for the activity of rheumatoid arthritis.

This study was established to answer 3 problems: 1) whether the application of a nicotinic acid ester locally was a valid test for rheumatoid activity; 2) whether the skin response was specific to the above nicotinic acid ester or could be obtained with other esters or nicotinic acid itself*; and 3) whether a refinement of the test was possible by an intracutaneous injection of the ester to assure accuracy of dosage and degree of response.

Method. Each subject was tested with 3 preparations and their controls at the same time. The volar surface of both forearms was used as the site of application. Tetrahydrofurfuryl ester of nicotinic acid in a 5% water miscible cream and its control were applied according to the technique described by Streitfeld and Saslaw[3]. One per cent 2(tetrahydropyranyl) methyl nicotinate made soluble in 1% propylene glycol in water, its control 1% propylene glycol in water, and 1% nicotinic acid and its diluting fluid were injected intracutaneously employing a tuberculin syringe equipped with a 27 gauge needle. The quantity injected never exceeded 0.1 cc. The subjects were observed continuously for 30 minutes but readings as to skin reaction were made at 5-minute intervals. The degree of erythema or blanching, the occurrence of localized edema and pruritus were noted. An atypical response was considered to be blanching or no visible erythema. The degree of erythema was arbitrarily graded from + to 4+. In a majority of the patients, at the same time the skin tests were performed, determination of the ESR (Westergren) and C-reactive protein reaction were performed.

The subjects comprised 2 groups: patients with, and without, rheumatoid arthritis, of the same age and sex distribution. The rheumatoid patients varied in stage of disease, classified according to the criteria of the American Rheumatism Association[2]. Twenty-six subjects were hospitalized and 21 were ambulatory. The nonrheumatoid controls comprised cases of osteoarthritis, gout, postural imbalance, fibrositis and nonarthritic conditions. Of this group, 10 were hospitalized and 41 were ambulatory. The majority of the arthritic patients were on salicylates as an analgesic agent, and 18 of the rheumatoid patients were receiving gold (Lauron) therapy. None of the subjects had any recent infection which would have perhaps influenced the ESR or C-reactive protein.

*Tetrahydrofurfuryl ester of nicotinic acid (Trafuril) was supplied by Ciba Pharmaceutical Products, Summit, N. J. Nicotinic acid, 2(tetrahydropyranyl) methyl nicotinate and diluents were supplied by Nepera Chemical Co., Inc., Nepera Park, Yonkers, N. Y.

Results. The skin response to all 3 preparations is summarized in Table 1. Although there were various differences in degree of erythema at the site of application of nicotinic acid or the 2 esters for any particular subject, the over-all response for all 3 preparations was the same. The absence of erythema, the response of greatest significance, occurred in approximately the same incidence for each preparation, regardless of presence or stage of rheumatoid arthritis. Similarly, there was no correlation between the type and degree of skin response attained with each preparation and the ESR or C-reactive protein reaction for either rheumatoid or control subjects. The intracutaneous technique offered no particular advantage except less likelihood of local pruritus. When the solutions of nicotinic acid and its esters were applied topically, the type of response was indistinguishable from one another.

TABLE 1.—SKIN RESPONSE TO NICOTINIC ACID AND ESTERS FOR RHEUMATOID AND CONTROL SUBJECTS

		Skin Response—Erythema					
		Tetrahydrofurfuryl Nicotinate		*2 (Tetrahydropyranyl) Methyl Nicotinate*		*Nicotinic Acid*	
Diagnosis	*No. of Subjects*	*None*	*Present*	*None*	*Present*	*None*	*Present*
Rheumatoid Arthritis							
Stage I	6	0	6	0	6	0	6
Stage II	9	5	4	4	5	4	5
Stage III	12	2	10	1	11	2	10
Stage IV	20	5	15	7	13	9	11
	47	12	35	12	35	15	32
Control	51	9	42	11	39	11	39

Discussion. The results are in contrast to those reported by Nassim and Banner[1]. We were unable to confirm the specificity of the skin response to a nicotinic ester for rheumatoid arthritis. As a diagnostic aid, it was therefore of no value. We were also unable to detect any correlation between the degree and type of response and the intensity of rheumatoid activity as measured by the ESR or C-reactive protein.

Streitfeld and Saslaw[3] reported a high correlation of the skin test with rheumatic fever and its activity, and a predictable erythematous response in normal controls. Although we cannot comment in regard to the efficacy of the test for rheumatic fever, we note that patients with rheumatoid arthritis do not have the same type of response. The significance of this is not clear, although it may indicate that there is a dissimilarity between the 2 diseases. There is, however, another factor which requires consideration. Our subjects were adults and the skin responses may differ from those in children. This might explain why our control group did not have the same high incidence of erythema as did that of Streitfeld and Saslaw[3].

Conclusions: 1. The skin response elicited by local application of nicotinic acid or its esters, tetrahydrofurfuryl nicotinate and 2(tetrahydropyranyl) methyl nicotinate, was the same for patients with and without rheumatoid arthritis.

2. A "typical" reaction of localized cutaneous hyperemia or edema or both, occurred in approximately 80% of the adult subjects regardless of rheumatic condition.

3. No correlation existed between the absence of erythema, degree of erythema and the stage of rheumatoid arthritis.

4. No correlation existed between the intensity of skin response and degree of rheumatoid activity as measured by ESR or C-reactive protein reaction.

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CONCLUSIONES IN INTERLINGUA

Responsa Cutanee Local a Acido Nicotinic e su Esteres Como Adjuta Diagnostic in Arthritis Rheumatoide

1. Le responsa cutanee evocate per le application local de acido nicotinic e su esteres, tetrahydrofurfurylo-nicotinato e 2(tetrahydropyranyl)-methylo-nicotinato, esseva le mesme in patientes con e sin arthritis rheumatoide.

2. Un "typic" reaction de localisate hyperemia o/e edema cutanee occurreva in circa 80 pro cento del subjectos adulte sin reguardo a lor condition rheumatic.

3. Nulle correlation existeva inter le absentia de erythema, le grado de erythema, e le stadio del arthritis rheumatoide.

4. Nulle correlation existeva inter le intensitate del responsa cutanee e le grado del activitate rheumatoide mesurate per le sedimentation erythrocytic o le reaction de proteina C-reactive.

SUMMARIO IN INTERLINGUA

(See page 627 for original article)

Le Relation de Cirrhosis del Hepate a Hypertension: Un Studio de 504 Casos de Cirrhosis del Hepate

Es presentate un revista de 504 patientes con cirrhosis del hepate. Le casos esseva dividite in quatro categorias secundo que lor diagnose esseva (1) de character clinic, (2) basate super datos bioptic, (3) basate super datos necroptic, e (4) de validitate dubitose. Nostre studio confirma clinicamente le conclusion del studios pathologic de Raaschou que hypertension arterial in humanos presuppone un functionamento hepatic que es normal o al plus levemente defective. Nostre studio demonstra in plus que le hypertension incontrate in patientes de cirrhosis post un stimulation stressante deberea esser considerate como physiologic plus tosto que como pathologic, e que hypertension renal es non prevenite per sever morbo hepatic. Finalmente, nos nota que un hypertension pre-existente pote reducer se a nivellos normal si le disveloppamento de cirrhosis interveni. Durante iste processo nos ha observate un reversion del proportion de albumina a globulina. Nos subleva le question del existentia de un globulina anormal con functiones in mantener o blocar hypertension "essential."

THE CLINICAL USE OF ERYTHROMYCIN*

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Despite the discovery of scores of antibiotics, the search for new ones continues. This is due in part to the frequent severe side-effects of present antibiotics, but mainly because no single antibiotic can be expected to serve for every infection that may arise. Indeed, if such an antibiotic were available, its use would be fraught with great danger. Frequently enough the trouble with the "broad-spectrum antibiotics" is that their spectrum is too broad. Only a minority of the bacteria present in the environment are pathogenic for man, and any antibiotic with too wide a range runs the risk of upsetting the balance in favor of the more pathogenic strains. Moreover, in their own struggle for survival, some bacteria, particularly the staphylococci, that originally were almost uniformly susceptible to the older antibiotics have become more and more resistant, requiring new drugs to combat them.

Erythromycin, one of the newest antibiotics, was discovered by McGuire and his co-workers 3 years ago[7]. It is produced by an actinomycete identified as *Streptomyces erythreus* and found originally in a soil sample collected in the Philippines during the course of a systematic search for new antibiotics. Erythromycin is a white crystalline material, basic in reaction, which readily forms salts with acids. It is poorly soluble in water (2 mg. per cc.) but extremely soluble in alcohol, acetone, chloroform, and ether. The molecular weight is estimated to be 733.9 to 735.9, and the empyrical formula is approximately $C_{37}H_{67}NO_{13}$. There is no sulphur, nitro, or benzene group in the formula. The activity and range of usefulness of erythromycin was reported by McGuire[7], Heilman and his associates[5], and Haight and Finland[3].

These early reports demonstrated that it is active against most Gram-positive organisms, a few Gram-negative organisms and a few viruses, rickettsiae and protozoa[7,10]. Erythromycin has a bactericidal as well as a bacteriostatic action, and exerts its effect only against multiplying bacteria[4,5]. Our own *in vitro* studies[6] agree in the main with those of other groups: erythromycin was found to be very active against virtually all naturally occurring strains of *Staphylococcus*

*This study was aided by grants from Eli Lilly and Company and the Dr. Simon Baruch Foundation for Research. The erythromycin (Ilotycin, Lilly) was supplied by Eli Lilly and Company. We are indebted to Mr. Joseph M. Vogel, B. Sc., for technical assistance.

aureus even though one-third to one-half of the strains were resistant to penicillin or other antibiotics. It was also very effective against pneumococci and all varieties of streptococci, but with the exception of *Hemophilus influenzae* had no inhibiting effect on the strains of Gram-negative organisms tested: *E. coli, B. Friedländer, Proteus vulgaris, Ps. aeruginosa, B. aerogenes,* and *Alkaligenes fecalis.*

Material and Methods. During the period from August 1, 1953, to June 20, 1954, erythromycin was used on the wards of the Fourth Medical Division of Bellevue Hospital in patients with a variety of infections.

The patients fell into three categories. There were 88 with pneumonia of all types, 20 with respiratory infections other than pneumonia, and a third category of 14 patients with miscellaneous infections (osteomyelitis, wound infections, Staphylococcus septicemia, furunculosis, cellulitis and erysipelas). Many were suffering from co-existing ailments such as vitamin deficiencies, chronic alcoholism, cirrhosis, general arteriosclerosis, and other conditions so common in a large city hospital like Bellevue.

On admission, all patients had a routine physical examination, blood count and urinalysis. Roentgenograms were taken at the beginning and during the course of the pneumonia. Blood, sputum, urine, and other cultures were performed when indicated.

Erythromycin is ordinarily given by mouth. The average adult oral dose, used in this series, was 400 mg. every 6 hours. Higher doses were used when necessary. The 200 mg. tablets coated with acid-resistant material were used in this study.

Serum levels were obtained in 13 patients 6 hours after receiving the drug by mouth. These were assayed by the method of Ziegler and McGuire[11]. The 6-hour serum levels ranged from 0.64 to 2.56 mcg. per cc., the average being 1.5. These were considered adequate therapeutic levels.

Six patients who were critically ill or could not take the medication by mouth received erythromycin intravenously in the form of erythromycin glucoheptonate. Five-hundred milligrams of the antibiotic mixed with 500 or 1,000 cc. of physiological saline or 5% dextrose was given every 6 hours. When the indications for parenteral administration were no longer present, the remaining treatment was given orally. Serum levels in 3 such cases, 2 hours after intravenous administration of erythromycin were 4.6, 2.56, and 1.6 mcg. respectively.

Three patients received the drug intramuscularly. The preparation used was early clinical trial material. It was too irritating for continued use as evidenced by a sterile abscess occurring in each of the 3 patients. Serum levels were not determined following the intramuscular material.

Results. PNEUMONIA. There were 88 patients representing all types of pneumonia as evidenced by physical examination, clinical course, and roentgenographic findings. The ages ranged from 15 to 86 years. As shown in Table 1, almost half the patients were over 50 years of age, and 25 of them were over 60. Sixty-eight were male and 20 female. Lobar pneumonia was present in 60 and bronchopneumonia in 28. In most instances, only one lobe was involved, but in 18 cases there was multilobar involvement. The following organisms were isolated from the sputum: pneumococcus, 15 cases; gamma streptococcus, 31; *Streptococcus viridans,* 5; mucoid streptococcus, 4; *Streptococcus hemolyticus,* 4; *Staphylococcus aureus,* 3; *Hemophilus influenzae,* 1, *B. Friedländer,* 1; and mixed organisms (different combinations of streptococci, pneumococci, and *Hemophilus influenzae*), 21. Three patients with primary atypical pneumonia were also treated with erythromycin.

The average duration of illness before hospitalization was approximately 5 days. The average length of treatment was 5.6 days. As a rule, patients who responded to erythromycin did so within 24 to 48 hours. In the 3 instances where the response was not prompt, therapy was changed or other antibiotics added. Such cases were considered treatment failures although there is the possibility that if more time had been allowed, the ultimate re-

sult would have been successful with the use of erythromycin alone. The change in antibiotic therapy did not appear to accelerate recovery.

There were 4 deaths. One of these was a 32-year-old male with pneumonia due to *B. Friedländer* type A, who was admitted on the seventh day of illness and died in less than 24 hours. Erythromycin was started before the sputum was examined, and he received only 400 mg. of the drug. Streptomycin, Gantrisin, and aureomycin were promptly added to the therapy without effect. At necropsy all 5 lobes were consolidated in varying degrees and abscesses were found in both lungs.

The second fatality occurred in a 28-year-old man who had been ill for 4 days prior to admission with pneumonia of both lower lobes. Pneumococci and gamma streptococci were cultured from the sputum. He became acutely cyanotic and the clinical and roentgenographic findings suggested the development of atelectasis of the left lung. Bronchoscopy revealed no intrinsic bronchial lesion. Culture of the bronchial secretions yielded a pure growth of *Proteus vulgaris*. There is no record of what medication this patient had before admission. Penicillin and aureomycin were substituted for erythromycin with no change in the downhill course. He died 7 days after admission. Permission for necropsy was refused.

The third death occurred in a 70-year-old man who had pneumonia of the right lower lobe, as well as hyper-

TABLE 1.—PNEUMONIA PATIENTS TREATED WITH ERYTHROMYCIN

Number of patients		88	
Age:	15–30	12	
	30–40	18	
	40–50	15	
	50–60	18	
	Over 60	25	
Sex:	Male	68	
	Female	20	
Type of pneumonia:	Lobar	60	
	Broncho-	28	
Number of lobes:	One	70	
	More then one	18	
Organism:	Pneumococcus	15	(2)*
	Gamma streptococcus	31	(2)
	Streptococcus viridans	5	(2)
	Mucoid streptococcus	4	
	Streptococcus hemolyticus	4	
	Staphylococcus aureus	3	(1)
	Hemophilus influenzæ	1	
	B. Friedländer	1	(1)
	Mixed organisms	21	(1)
	Primary atypical	3	
Recovered		84	
Died		4**	
Therapy failures		3	
Side reactions		7	
Side reactions requiring cessation of therapy		1	
Complications:	Pleural effusion	3	
	Delayed resolution	3***	

*The figures in brackets represent cases with positive blood cultures.
** Only one of these was a pneumonia death following adequate erythromycin therapy (see text).
*** Two of these patients are included in the number that had pleural effusion.

tensive and arteriosclerotic heart disease. He responded promptly to therapy and appeared to be convalescing. However, on the sixth hospital day, he had a cerebral thrombosis with right hemiplegia and aphasia. Death occurred one week later.

The fourth to die was a 63-year-old man who had a cerebral vascular accident complicated by pneumonia with bacteremia due to *Streptococcus viridians*. His pneumonia appeared to be clearing under therapy with erythromycin when, on the fifth day, he developed a massive hematemesis and melena and died in spite of repeated transfusions. At necropsy, three duodenal ulcers were found. There is no reason to suspect that the ulcers were related to the therapy. One might speculate, however, that they may have resulted from pituitary-adrenal stimulation from the fever and disease products.

One patient with pneumonia and pleural effusion due to *Hemophilus influenzae* was responding rather slowly. Penicillin and tetracycline were substituted with no evidence of acceleration in the rate of recovery. Therapy was completed after 5 weeks. This case was considered a treatment failure.

Another patient with pneumonia due to mixed organisms was admitted in a state bordering on shock. She received erythromycin for 2 days following which penicillin and terramycin were also given. Her recovery was complete in 3 weeks.

A third treatment failure was a patient with pneumococcic pneumonia and pleural effusion. A roentgenographic study 2 weeks after admission showed a translucent area which may have been either an abscess or central clearing of the pneumonic process. Bronchoscopy showed no bronchial lesion, and the sputum was not foul. Penicillin was added to therapy, and the pulmonary lesion gradually cleared after several more weeks.

These 3 treatment failures had delayed resolution, requiring longer than 4 weeks for the pneumonia to clear. Three of the patients described above had pleural effusions. The effusion in each instance cleared during the hospital stay. Empyema did not develop in any patient in this series.

One patient who was admitted with a nonputrid lung abscess following pneumonia and who did not improve following therapy with penicillin and aureomycin, was treated with erythromycin. He showed great improvement after one week of therapy but left the hospital before the lesion was completely resolved.

Illustrative cases are shown in Figs. 1 to 6. The legends are self-explanatory.

It is interesting to note that the clinical results corresponded with the *in vitro* studies. Virtually all the organisms cultured from these pneumonia patients showed a high degree of sensitivity to erythromycin.

Our results of therapy of pneumococcic pneumonia with erythromycin are shown in Table 1. These findings agree with those reported by Haight and Finland[3], Romansky, Nasou and Ritts[8], Waddington, Maple and Kirby[9], and Austrian and Rosenblum[1]. Bunn and Cook[2], however, found the drug to be ineffective. It seems likely that their unfavorable results were due to inadequate concentrations of the antibiotic in the serum since they were using gelatin capsules instead of acid-resistant coated tablets. Their "failures" did not respond to penicillin.

OTHER RESPIRATORY INFECTIONS. There were 20 patients with respiratory infections other than pneumonia. The diagnosis and infecting organisms are shown in Table 2. Patients with pharyngitis and tonsillitis due to the usual

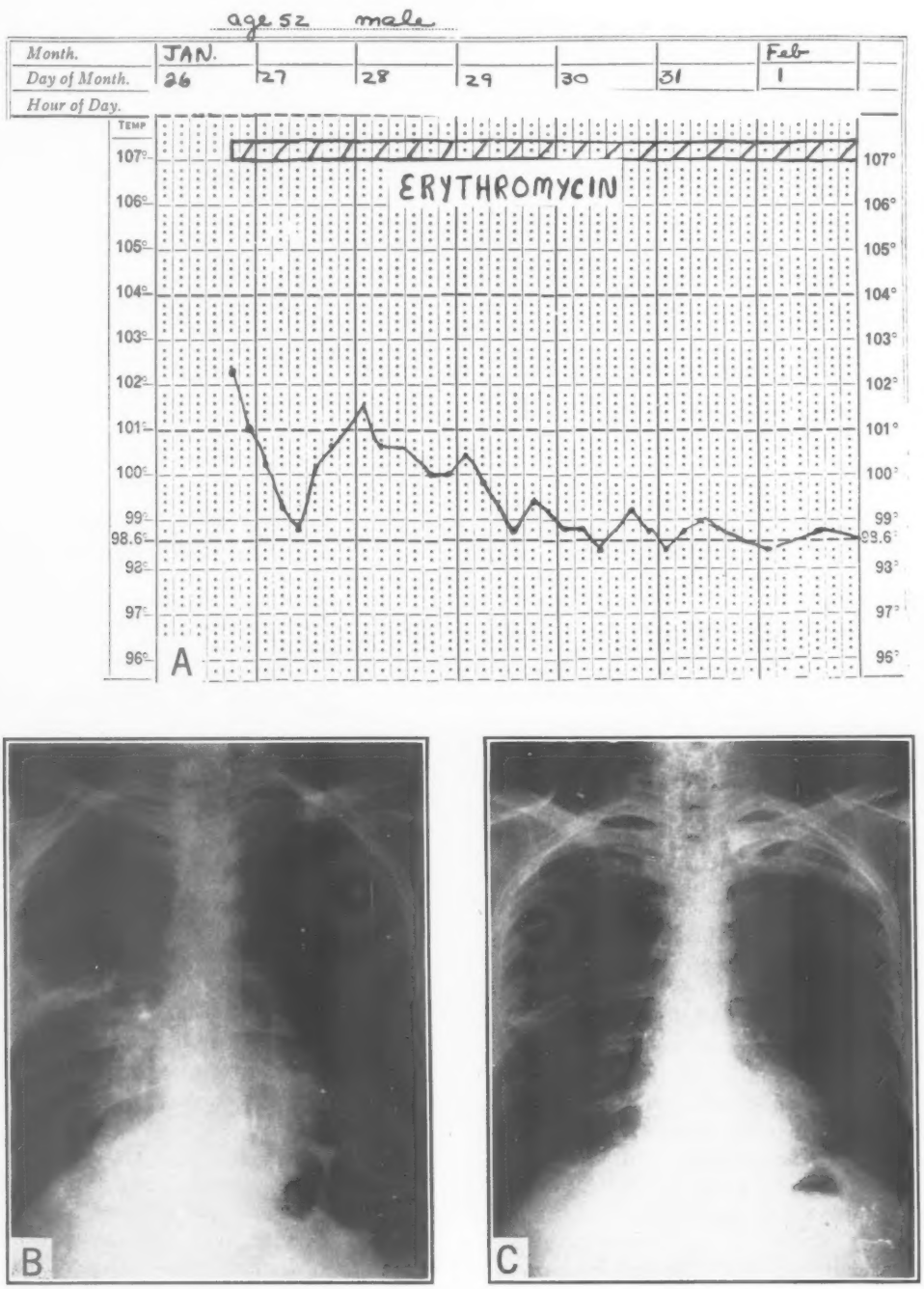
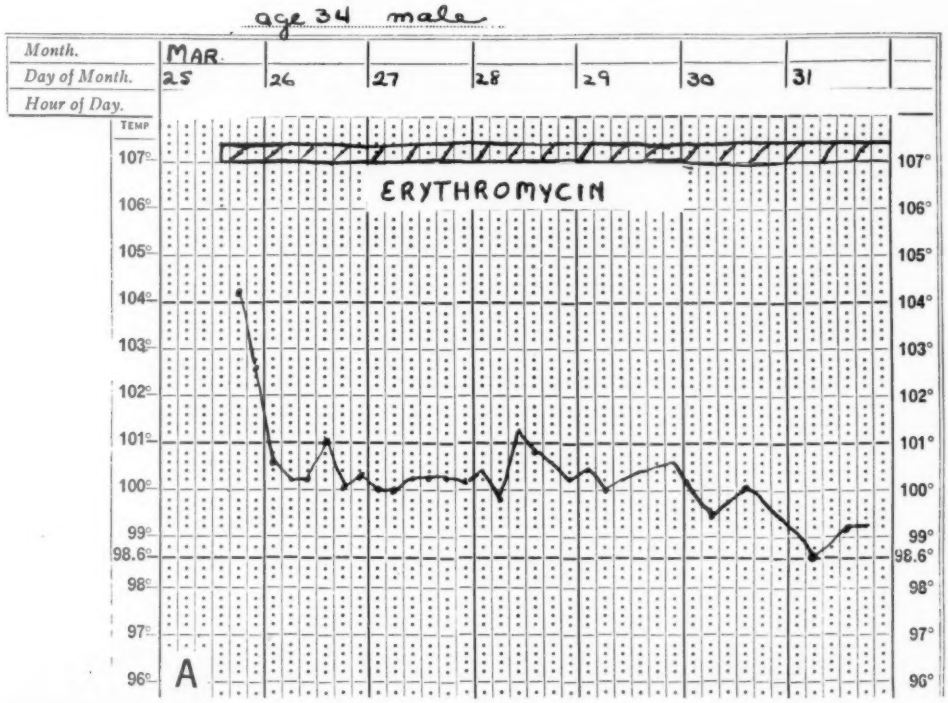


Fig. 1.—CASE 1: (*A*) Temperature chart showing resolution by lysis following treatment with erythromycin. Sputum showed Gamma streptococci. (*B*) Film showing bronchopneumonia of right lower lobe. (*C*) Roentgenographic study 10 days later shows almost complete clearing.



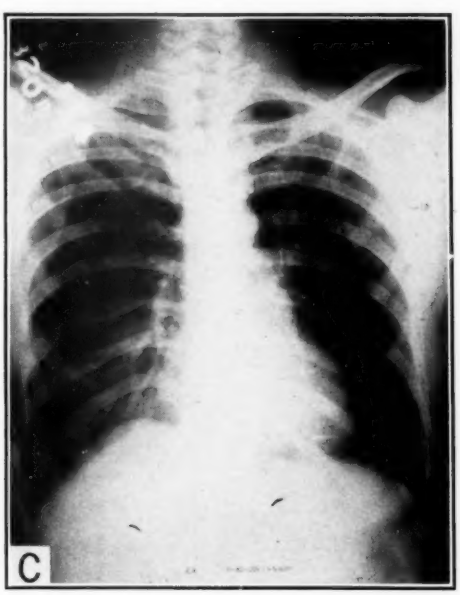


Fig. 2.—CASE 2: (*A*) Treated with erythromycin, prompt crisis. (*B*) Lobar pneumonia of right lower lobe. Blood culture showed *Str. viridans*. (*C*) Roentgenographic study 8 days later, almost complete resolution.

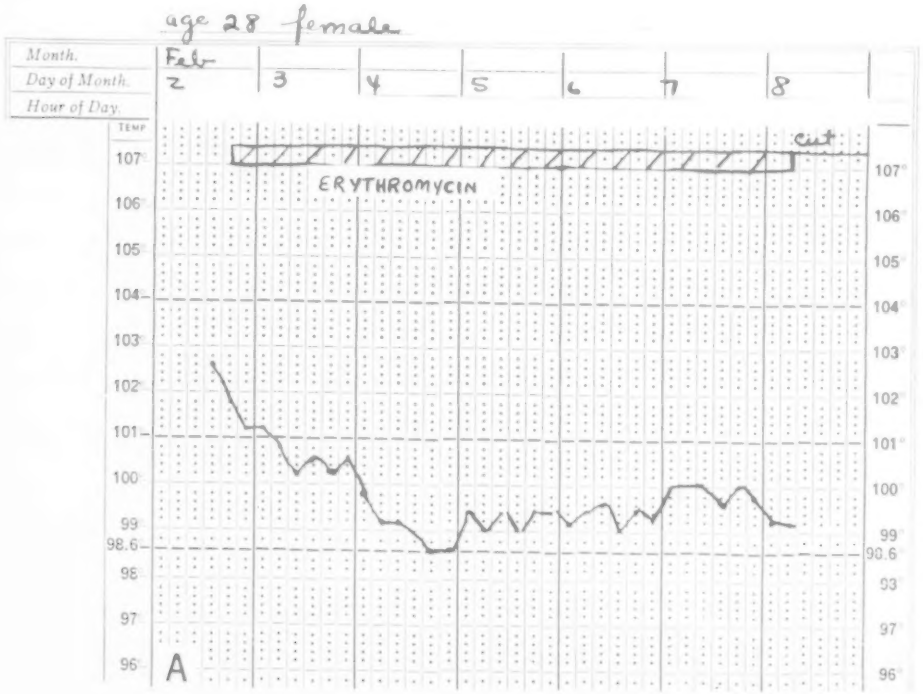
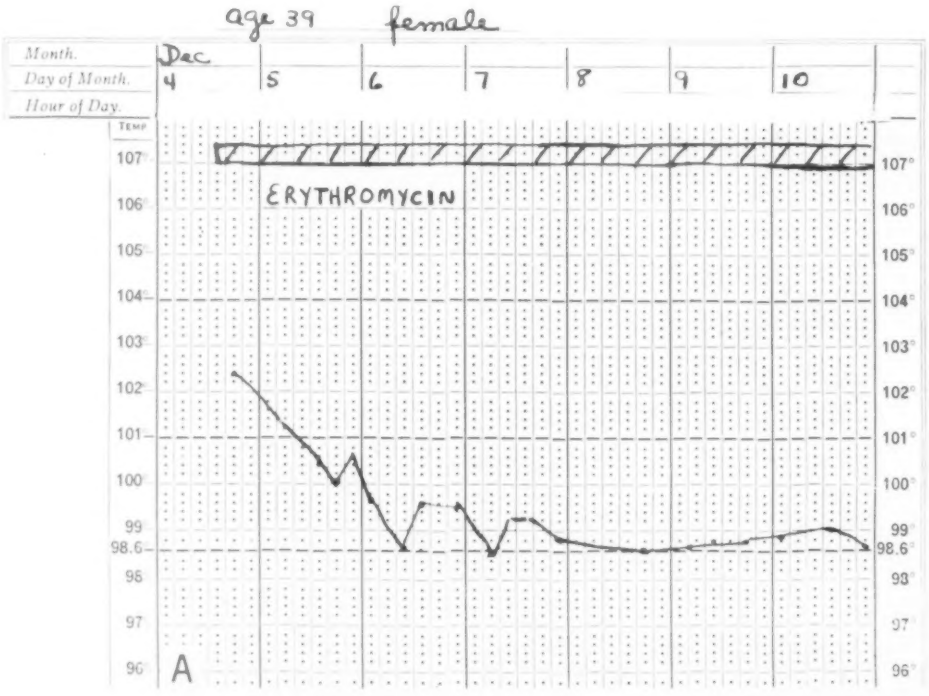


Fig. 3.—CASE 3: (*A*) Temperature chart of patient with pneumonia due to mucoid streptococci. Fever (and toxemia) subsided 36 hours after treatment started. (*B*) Lobar pneumonia of left lower lobe. (*C*) Roentgenographic study 9 days later showed complete resolution of the pneumonia.



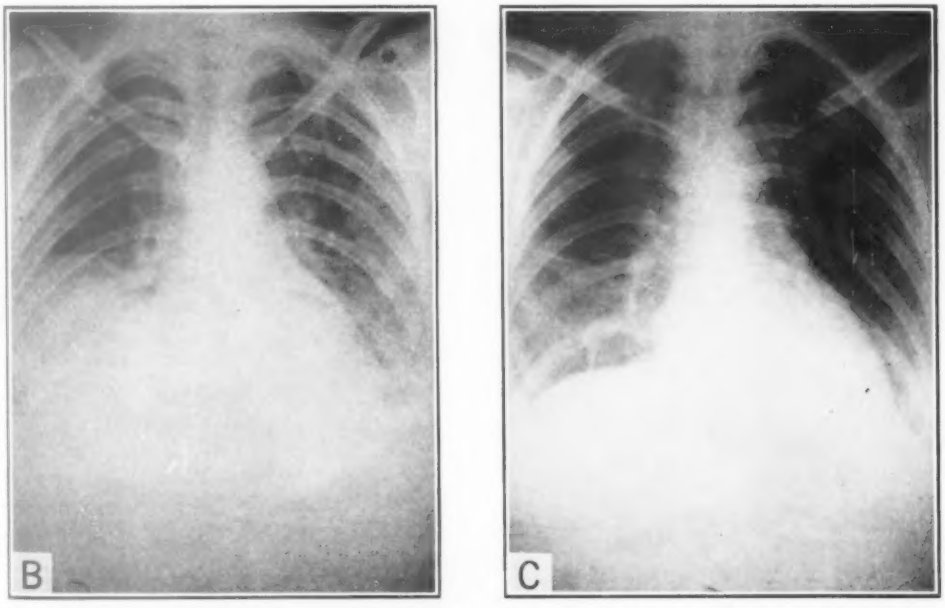


Fig. 4.—CASE 4: (*A*) Temperature chart showing drop of fever in 36 hours. Hemolytic *Staphylococcus aureus* in pure culture in the sputum. Patient was clinically much more ill than height of fever would indicate. (*B*) Lobar pneumonia of right lower lobe. (*C*) Roentgenographic study 8 days later showing considerable clearing.

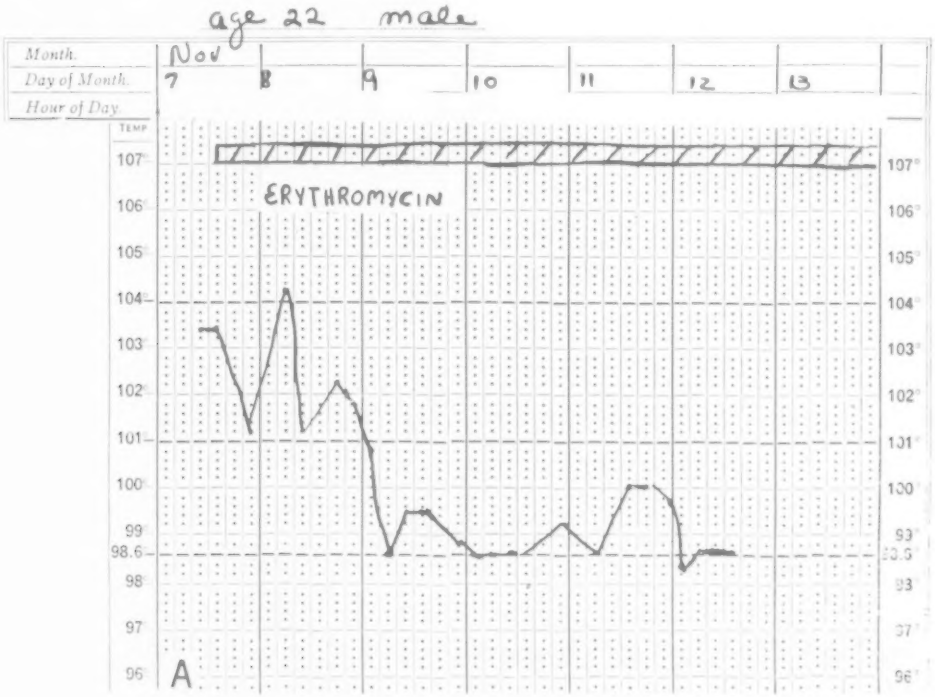


Fig. 5.—CASE 5: (*A*) Temperature returned to normal in less than 48 hours after therapy started. (*B*) Pneumonia of right lower and middle lobe. Sputum contained *Str. hemolyticus*. (*C*) Roentgenographic study 2 weeks after admission shows lungs to be clear.

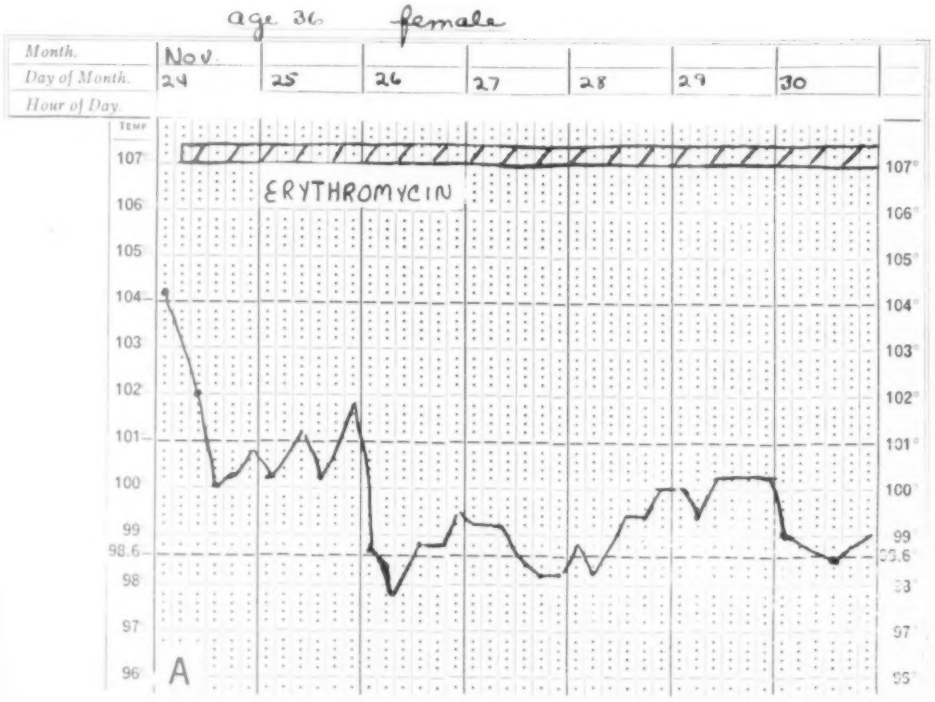


Fig. 6.—CASE 6: (*A*) Fever chart demonstrating rapid response to erythromycin. Sputum and blood culture were positive for pneumococci. (*B*) Pneumonia of right lower and middle lobe. (*C*) Roentgenographic study one week later showing considerable resolution of the pneumonia.

Gram-positive organisms showed a prompt drop in fever and relief of symptoms. Staphylococcic infections of the middle ear responded favorably within a few days. One patient had a recurrence of middle ear infection from which *Alkaligenes fecalis* was cultured. This did not respond to a second course of erythromycin therapy. Seven patients with bronchitis responded favorably. One of these patients had *Staphylococcus aureus* bacteremia which responded after 3 weeks of erythromycin therapy. One patient with bronchiectasis showing pneumococci and streptococci in the sputum improved considerably. Results of therapy are incomplete since the patient did not return for re-examination after leaving the hospital.

One of the most interesting problems was that of a 40-year-old female with carcinoma of the lung and empyema. She had received penicillin for approximately 2 weeks without improvement. Culture of pus obtained from the pleural cavity showed a pure growth of *Streptococcus hemolyticus* which was resistant to penicillin but was very sensitive to erythromycin. She was treated with erythromycin for 10 days with excellent results. Only a small amount of fluid could be obtained by thoracentesis at the end of this time, and this was clear and sterile.

MISCELLANEOUS INFECTIONS. There were 14 other patients with miscellaneous infections, all of which were treated successfully with erythromycin as shown in Table 3. Three patients with furunculosis responded rapidly and did not require surgical drainage. Two patients with purulent blepharitis did equally well. One patient with staphylococcic osteomyelitis of the radius and a draining sinus of several years' duration had previously been treated unsuccessfully with penicillin, aureomycin, terramycin, and sulfonamides. Within one week after starting erythromycin, the drainage stopped, and in a few weeks the sinus closed. She has had no recurrence.

One 30-year-old man with a reticulum cell sarcoma and great enlargement of the spleen had a splenectomy on December 15, 1953. Soon after he developed a subdiaphragmatic abscess. This was drained surgically, and culture showed *Staphylococcus aureus* and *Pseudomonas aeruginosa*. He received erythromycin and in several days the drainage of pus decreased considerably and it became thinner. Culture now showed only *Pseudomonas aeruginosa* which was resistant to erythromycin. Nevertheless, the abscess and sinus tract healed, and the patient was discharged. He received radiation therapy for the sarcoma and is still alive.

One patient who was a drug addict was admitted with tetanus due to self-administration of heroin. His clinical course was very unusual, and Dr. William S. Tillett and Dr. Maria Stack of the Third Medical Division of Bellevue Hospital who treated him will report the case in detail. He received tetanus antitoxin, streptomycin and penicillin but continued to run a septic temperature. Several days after admission, cultures of the blood and spinal fluid yielded *Staphylococcus aureus*. Erythromycin was given intravenously for a week. The temperature dropped to normal and blood and spinal fluid cultures were sterile. He recovered with no further complications.

There were 2 patients with the characteristic rash of erysipelas. One of them had bacteremia with *Streptococcus hemolyticus*. Both improved rapidly after erythromycin was given. Three patients with cellulitis due to *Staphylococcus aureus* had a similar good response. One man with an infected human bite of the hand received

TABLE 2.—OTHER RESPIRATORY INFECTIONS TREATED WITH ERYTHROMYCIN

Diagnosis	*Number of Cases*	*Organism*	*Result*		*Toxic Reactions*	*Remarks*
			Successful	*Failure*		
Acute pharyngitis	5	Gamma strep. 4	4	—	—	Prompt drop in fever and relief of symptoms
		Pneumococcus and *Staph. aureus* 1	1	—	—	
Acute tonsillitis	2	*Str. hemolyticus* 1	1	—	—	Prompt drop in fever and relief of symptoms
		Gamma streptococcus 1	1	—	—	
Abscess of vestibule of nose	2	*Staph. aureus* 1	1	—	—	Prompt drop in fever and relief of symptoms
		Not cultured 1	1	—	—	
Otitis media	5	*Staph. aureus* 4	4	—	—	
		Alkaligenes fecalis 1	—	1	—	
Acute and chronic bronchitis	7	Gamma streptococcus 3	3	—	—	
		H. influenzæ 1	1	—	1 had diarrhea	
		Mixed organisms 3	3	—		
Bronchiectasis	1	Pneumococci and streptococci 1	1	—	—	No follow-up
Empyema	1	*Str. hemolyticus*	1	—	—	This patient had cancer of lung and empyema. Empyema previously treated with penicillin without effect

TABLE 3.—MISCELLANEOUS INFECTIONS TREATED WITH ERYTHROMYCIN

Diagnosis	*Number of Cases*	*Organism*	*Results*		*Remarks*
			Successful	*Failure*	
Furunculosis	3	*Staph. aureus* 3	3	—	One patient had prior ineffective treatment with penicillin. His organisms were resistant *in vitro* to penicillin, sensitive to erythromycin
Blepharitis	2	*Staph. aureus* 1	2	—	
		Not cultured 1	—	—	
Chronic osteomyelitis	1	*Staph. aureus* 1	1	—	Prior treatment with penicillin, aureomycin, terramycin and sulfonamides failed
Subdiaphragmatic abscess	1	*Staph. aureus* 1	1	—	This man had reticulum cell sarcoma; developed abscess after splenectomy
Staph. septicemia and meningitis	1	*Staph. aureus* 1	1	—	Drug addict. Treated with tetanus antitoxin, streptomycin, and penicillin. Developed Staph. septicemia which responded to erythromycin
Erysipelas	2	*Str. hemolyticus* 1	2	—	One patient had *Str. hemolyticus* septicemia
		Not cultured 1	—	—	
Cellulitis	3	*Staph. aureus* 3	3	—	
Human bite	1	Not cultured	1	—	

900,000 units of procaine penicillin intramuscularly. The wound was not cultured. On the following day, the hand became more swollen, red streaks were seen on the forearm, and the axillary nodes were enlarged. Erythromycin was given in the usual dosage and in less than 48 hours the infection had subsided.

DRUG TOXICITY. Erythromycin was very well tolerated by most patients. One patient developed an erythematous rash during treatment. However, she had a history of allergy and previous eruptions without obvious cause, and there was doubt that the rash was related to erythromycin. One patient had nausea and vomiting after taking erythromycin. One patient had fever which could not be accounted for by the physical and laboratory findings and may have been a reaction to erythromycin. Four patients had loose bowel movements, but in only one was it sufficiently troublesome to necessitate stopping the drug.

There were no reactions from the intravenous use of erythromycin in 6 patients. Three patients who received clinical trial erythromycin intramuscularly developed painful sterile abscesses which cleared up without drainage. This intramuscular preparation was experimental and will not be distributed for general use. The material has been discontinued by the manufacturer.

Eight patients had delirium during the course of treatment. However, all of them had a history of chronic alcoholism. The tendency of acute illness to precipitate confused states in such patients is well known. Three patients with this symptom were continued on the antibiotic, and the delirium cleared up as the infection came under control. Two of the patients who had had delirium were again given erythromycin for several days after recovering from their acute illness, and they manifested no reaction. Dr. Noel Galen and Dr. Marvin Stern of the Psychiatric Division studied these patients and believed the confused state was due to the acute illness in patients with an alcoholic background.

Summary. Eighty-eight patients with pneumonia due to a variety of organisms were treated with 400 mg. of erythromycin every 6 hours. The response was favorable whether the pneumonia was due to the pneumococcus, streptococcus, staphylococcus, or mixed organisms. The clinical results corresponded with *in vitro* sensitivity studies.

Only one patient could be considered a pneumonia death following adequate erythromycin therapy. Using strict criteria, 3 other patients are considered treatment failures.

Twenty patients with respiratory infections other than pneumonia were treated. These included cases of pharyngitis, tonsillitis, otitis media, bronchitis, bronchiectasis and empyema. All showed prompt improvement and recovery except for one patient with otitis media due to *Alkaligenes fecalis*.

Fourteen patients with miscellaneous infections were treated successfully with erythromycin. These included furunculosis, blepharitis, osteomyelitis, subdiaphragmatic abscess, staphylococcus septicemia and meningitis, erysipelas, and cellulitis.

Erythromycin showed a low incidence of toxic reactions. One patient developed a rash, another had fever which may have been due to drug reaction. One patient complained of nausea and vomiting after taking erythromycin, and 4 patients had loose bowel movements under therapy. Of the 122 patients receiving 400 mg. every 6 hours of erythromycin, it was necessary to stop therapy in one patient because of side-effects.

Eight patients with a previous history of alcoholism had delirium during the course of treatment. It was concluded that the confused state was typical of that encountered with acute severe illness in patients with an alcoholic background.

In the staphylococcic and streptococcic infections, other than pneumonias, without exception the results of treatment with erythromycin were excellent. This corresponds with the experience of other workers. In view of the high incidence of strains of staphylococci resistant to penicillin and other antibiotics, erythromycin appears to be the drug of choice in the treatment of most acute staphylococcic infections.

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(Interlingua on page 713)

SUMMARIO IN INTERLINGUA

(See page 636 for original article)

Le Effecto del Administration de Sitosterol Super le Nivello Seral de Cholesterol e Super le Configuration Electrophoretic del Lipoproteinas

1. Le administration de beta-sitosterol a patientes sin restrictiones dietari resultava in un reduction del concentration seral de cholesterol sin reguardo al nivello initial. Nulle indesirabile effectos lateral esseva notate. Nulle patiente experientiava un significative alteration de peso.

2. Le minimo efficace de sitosterol in un curso de 4 septimanas esseva un dosage diurne de 10 g. Le maximo tolerate non esseva determinate.

3. In 2 patientes con un stricte dieta a basse contento de grassia, le addition de sitosterol resultava in un reduction additional del cholesterol seral.

4. In le presentia de significative reductiones del concentration de cholesterol seral, certe alterationes se manifestava in le configurationes electrophoretic del lipoproteinas. In comparation con configurationes de controlo, le configurationes post tractamento revelava (a) un reduction del large zona de lipido beta, includente le alte summitate e extendite usque al latere cathodic ab le puncto de application, e (b) nulle significative alteration in le fraction de lipido alpha o in le configuration proteinic.

PROGRESS
OF
MEDICAL SCIENCE

PEDIATRICS

UNDER THE CHARGE OF
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A REVIEW OF PORPHYRIN METABOLISM WITH SPECIAL REFERENCE TO CHILDHOOD

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ALTHOUGH the scientific literature of the past century is liberally sprinkled with articles about porphyrins and their functions, few authors have commented upon the occurrence and significance of porphyrins in children. Most of the literature is descriptive, and is limited to diseases of adults exhibiting coproporphyrinuria, or to the rare disorders, the porphyrias.

Our concept of the biogenesis and metabolic functions of the porphyrins and porphyrin-containing compounds has been revolutionized since the advent of isotopic tracers and other modern biochemical tools. Knowledge gained by use of these techniques has permitted replacement of the purely descriptive approach to the porphyrinopathies by careful investigation of the cellular mechanisms involved and the factors influencing them. On the basis of this knowledge, it is now accepted that the abnormal porphyrin excretions seen in the porphyrias and porphyrinurias reflect defective porphyrin *synthesis*. Accordingly, studies aimed at identifying the biochemical lesion(s) underlying these disorders should lead to a better understanding of their pathogenesis. Physiologically, porphyrin complexes are so inextricably involved in cellular oxidations and other important metabolic functions

that physicians dealing with either children or adults should be familiar with them.

This review has been limited to events occurring within the last decade and the reader's attention is invited to several publications providing access to earlier medical literature[13,27,29,44,61,62,77,85,99,131-133,135,138,147]. Speculation has been avoided wherever possible and material limited to data already in print or formally presented at scientific meetings. Clinical implications of disturbed porphyrin metabolism in children are emphasized.

The Significance of Porphyrins in Nature. In both the plant and animal kingdoms, many vital cellular processes are mediated by porphyrin complexes. Photosynthesis, a series of reactions carried out by plants in which solar energy is utilized to form organic material, requires the green magnesium porphyrin, chlorophyll (Fig. 1). Products of photosynthesis serve, in turn, as essential sources of energy for animal life and the release of energy from these foodstuffs by animal cells depends upon iron protoporphyrin (heme) structures (Fig. 1). These structures include the heme proteins hemoglobin and myoglobin and several important enzymes (catalase, other peroxidases, and the cytochromes). The relationship between the metalloporphyrin complexes occurring in plants and animals is summarized by the following equation:

$$CO_2 + H_2O + \text{Energy} \underset{\text{Heme}}{\overset{\text{Chlorophyll}}{\rightleftharpoons}} O_2 + \text{Organic Compounds (Food)}$$

Rimington[99] has drawn attention to Oparin's suggestion that the earth's atmosphere originally was devoid of oxygen. If we accept this hypothesis, it follows that chlorophyll was probably one of the first catalysts to appear in living organisms with the gradual oxygenation of the atmosphere ensuing.

Porphyrin complexes have been identified in almost all unicellular organisms and occur in the hemoglobins, erythrocruorins, and chlorocruorins of invertebrates. Petroleum deposits contain a vanadium porphyrin, indicating that the organic precursors of oil were rich in these substances. Quite recently, a porphyrin has been identified as part of a molybdenum flavoprotein functioning in electron transport[83,84], and evidence of a cobalt porphyrin moiety in vitamin B_{12} has been presented[14].

Thus, it is clear that porphyrins play a major role in metabolic processes and detailed elucidation of their biosynthesis and functions cannot fail to be of value to all students of human physiology and biochemistry.

Structure and Nomenclature of Porphyrins. Porphyrins are cyclic tetrapyrroles in which the four pyrrole nuclei are united by four methene (=CH—) bridges. The methene bridges participate in a resonating ring within the porphyrin molecule which is responsible for many of the unusual physical-chemical properties of this class of compounds. If one methene bridge is opened, for example that between rings number one and two (Fig. 2), the cyclic structure is destroyed and a bile pigment results.

Porphyrins differ in the types of substituents attached to the pyrrole rings and the positions of these substituents in relation to each other give rise to different isomeric configurations. The isomer types of the porphyrins refer to the relationship they bear to the four etioporphyrins originally synthesized by Hans Fischer[39] which are

illustrated in Fig. 3. Only type I and type III porphyrins have thus far been identified in nature.

Structures of the naturally-occurring porphyrins, coproporphyrin, uroporphyrin, and protoporphyrin appear in Fig. 2. Coproporphyrin and uroporphyrin bear only two types of substituents, the former containing four methyl and four propionic acid radicals, while the latter contains four acetic acid and four propionic acid residues, and thus have only four possible isomers. Protoporphyrin, however, bears three types of substituents, two vinyl, two methyl, and four propionic acid radicals, and has 15 possible isomers. The protoporphyrin which combines with an atom of iron to form heme is derived from the type III etioporphyrin and is called protoporphyrin 9. In this connection, it is interesting to note that the porphyrin of chlorophyll also has the type III configuration (Fig. 1).

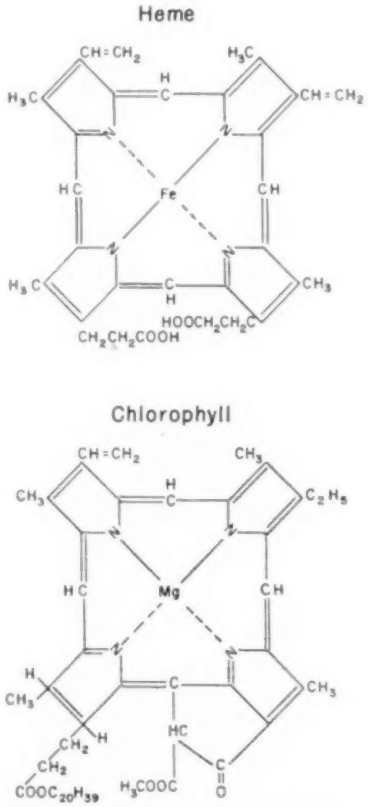


Fig. 1.—Structures of heme and chlorophyll, the most important porphyrins of the animal and plant kingdoms respectively.

This brief consideration of structure and nomenclature necessarily precedes any discussion of the biochemical significance of clinical disorders in porphyrin metabolism. The reader may find occasional reference to the figures advantageous.

Biosynthesis of Porphyrins and

Heme. The discovery of Shemin and Rittenberg that a simple amino acid, glycine, is preferentially utilized for heme synthesis *in vivo* constitutes one of the most important recent advances in porphyrin biochemistry[117,118]. It was soon learned that the carboxyl carbon from glycine does not participate in heme synthesis[56,95] but that the nitrogen and methyl carbon are characteristically distributed in the porphyrin molecule along with carbon atoms from another source, now known to be succinic acid[3,88,119,120]. Recently, Shemin and Russell have shown that "active" succinate condenses on the alpha-carbon of glycine, ultimately giving rise to delta-aminolevulinic acid, a compound which serves as the source for all carbon and nitrogen atoms in the porphyrin molecule[121,124]. Two molecules of this porphyrin precursor condense to give the monopyrrole, porphobilinogen, recently crystallized from human urine by Westall[153] and characterized structurally by Cookson and Rimington[25]. Direct evidence for the existence of this reaction (step "C", Fig. 4) has been obtained using a purified enzyme isolated from duck erythrocytes. This preparation readily accomplishes step "C" (Fig. 4) giving

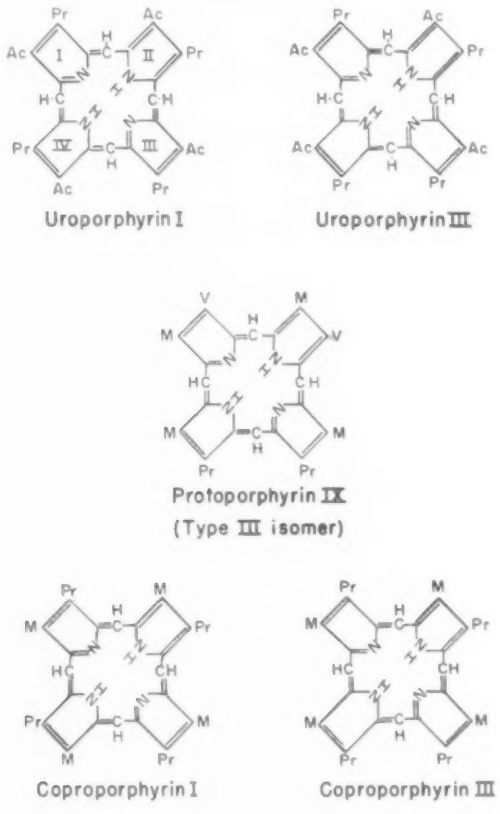


Fig. 2.—Structures of some physiologically and pathologically important porphyrins.

rise to porphobilinogen having twice the molar radioactivity of the isotopic delta-aminolevulinic acid used as substrate. Shemin has proposed a mechanism for the biosynthesis of porphyrins from the monopyrrole involving formation of a tripyrrylmethane as the first step. Subsequent cleavage of this compound at either of two points may give rise to two different dipyrrylmethanes which, in turn, may condense to form porphyrins of either the type I or type III series. For example, if two like dipyrrylmethanes react, a type I

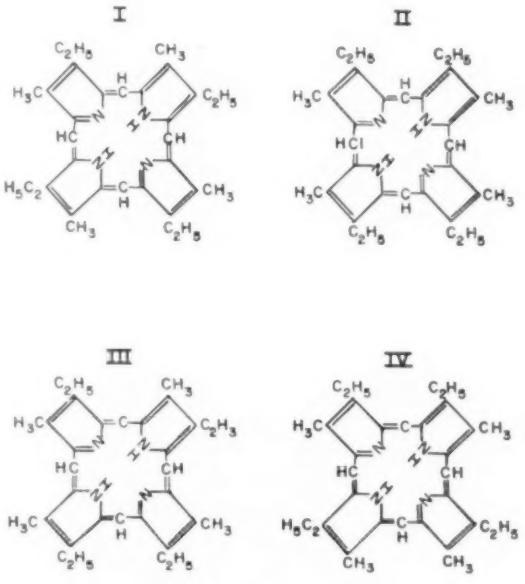


Fig. 3.—Structures of the four artificial porphyrins, the etioporphyrins, prepared by Hans Fischer[39] to which the isomeric configurations of all other porphyrins are referred.

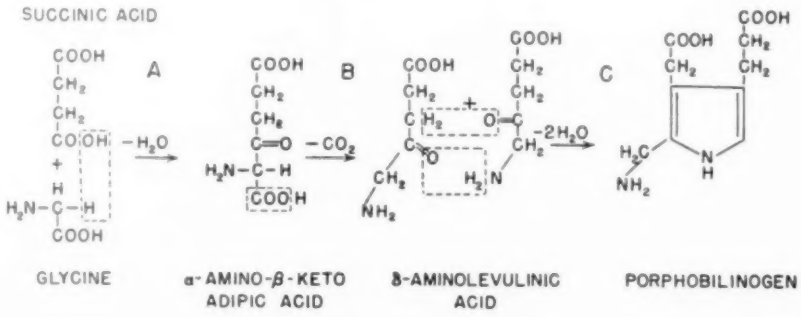


Fig. 4.—The reaction sequence leading from succinate and glycine to porphobilinogen, the monopyrrole precursor of porphyrins.

isomer results; if the dipyrrylmethanes are different, a type III isomer is formed[124].

Several studies of porphyria patients indicate that the uroporphyrin and coproporphyrin excreted in this disease are formed from glycine and succinate by a sequence much like that leading to protoporphyrin[53,54,57,58,79,80,89]. However, the roles of these different porphyrins in the biosynthetic process remain to be clarified. There is little

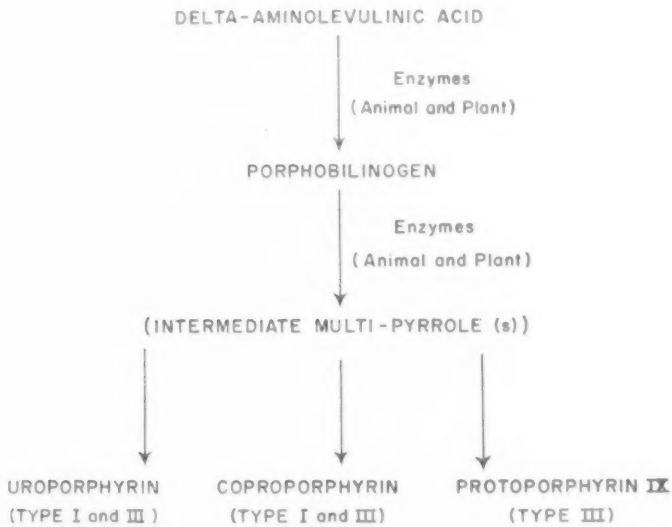


Fig. 5.—A schematic representation of present knowledge of tetrapyrrole synthesis from δ-aminolevulinic acid.

direct evidence to support the hypothesis that uroporphyrin and coproporphyrin are true protoporphyrin precursors. Experiments in progress may reveal the existence of other multipyrroles which act as precursors of the porphyrins just mentioned. In fact, evidence has been presented that hematoporphyrin and reduced forms of other tetrapyrroles may be precursors of heme[12,31,51]. Although rabbit bone marrow preparations have been reported to form protoporphyrin *in vitro* from labeled uroporphyrin III[102], this finding has not been confirmed. Experiments using rat liver homogenates[116] failed to demonstrate incorporation of isotopic uroporphyrin or coproporphyrin into protoporphyrin. Further data suggesting that coproporphyrin III is not a direct precursor of protoporphyrin have been obtained using a yeast unable to synthesize glycine[157]. Since the yeast formed protoporphyrin if glycine were added to the medium, it would be expected that the addition of any intermediate in the direct pathway from glycine to protoporphyrin would have a similar effect. However, addition of coproporphyrin III failed to induce protoporphyrin synthesis. This is consistent with the observation that C^{14} labeled coproporphyrin III is not converted to protoporphyrin by duck erythrocyte preparations[124].

At present, much interest centers about the enzymic conversion of delta-aminolevulinic acid to porphobilinogen

and, in turn, to uroporphyrin, coproporphyrin, and protoporphyrin (Fig. 5). The enzymes mediating these reactions and the optimum conditions for each step are being investigated in several *in vitro* systems including avian erythrocytes[28,33,50,90,108,122], a green alga (Chlorella)[11], mammalian liver preparations[45,116], avian liver powder[109], and spinach leaf extract[12].

Although it has been assumed that heme is formed by the incorporation of iron into protoporphyrin, there is a distressing lack of direct evidence to support this assumption. Certainly it is conceivable that iron may enter the tetrapyrrole ring at an earlier stage in porphyrin biosynthesis and be present while final alterations in the side chains shape the heme molecule. A better understanding of this aspect of porphyrin and heme synthesis may lead to practical clinical solutions for some of the obscure anemias in which hemoglobin formation appears to be defective.

Urinary and Erythrocyte Porphyrins in Normal Children. URINARY PORPHYRINS. Until recently only occasional urinary coproporphyrin values for children have been reported, and these usually have been included with exhaustive studies of adults. Significantly different analytical methods were used in each study. However, since the advent of the excellent procedure of Schwartz, Zieve and Watson[111], which converts coproporphyrin precursors to porphyrin before quantitation[30,96,144], variability in results stemming from the use of different analytical techniques need no longer present a problem.

A direct relationship between body weight and urinary coproporphyrin excretion was first established by a study including data from 17 normal persons, 7 of whom were children[125]. This observation was confirmed in 94 apparently normal boys between the ages of 6 and 16 years[63]. Their daily urinary coproporphyrin excretions correlated more closely with body weight than body surface area. These values are compared with our own[92] in Table 1.

TABLE 1.—MEAN URINARY COPROPORPHYRIN EXCRETION

(μg/24 Hours)

	Normal Boys			
Weight in Pounds	*Hsia and Page*[63]		*Neve and Aldrich*[92]	
	Mean	*S.D.*	*Mean*	*S.D.*
41–60	38.5	17.9	..	..
61–80	47.4	19.5	75.6	6.8
81–100	48.5	23.6	94.1	7.1
101–110	..	..	113.2	9.8
101–120	62.8	29.4	..	..
121–170	66.2	32.8	..	..

The ratio of urinary coproporphyrin isomers (I and III) can be determined by a fluorescence quenching technique[110]. We have found that over 90% of the urinary coproporphyrin excreted by normal children is the type III isomer[92] and have repeatedly failed to demonstrate appreciable amounts of type I coproporphyrin. There is a difference of opinion regarding the normal distribution of coproporphyrin isomers in adults[24,140]. Our findings, however, agree with those of Comfort, Moore, and Weatherall[24].

Although no quantitative data on the urinary uroporphyrin excretions of normal children have been published, observations made in our laboratory indicate that traces of uroporphyrin are actually present. Since traces of uroporphyrin are present in normal adult urine[24,38,78,93,99,115], it is reasonable to assume that it also is present in childhood. This matter deserves attention because it was believed for many years that uroporphyrin was excreted only in porphyria. This view must now be modified, at least in the case of adults, to fit the facts, which indicate that *excessive* uroporphyrin excretion is characteristic of porphyria. Furthermore, it has been established that adults suffering from a variety of serious illnesses excrete uroporphyrin in amounts larger than the traces customarily found[154]. Thus, it may be concluded that moderate uroporphyrinuria under such conditions does not necessarily indicate that the individual suffers from an inborn metabolic error.

ERYTHROCYTE PORPHYRINS. Free protoporphyrin was identified as a normal constituent of human red blood cells by van den Bergh and Hyman[134]. The pigment is not bound to metal and its concentration varies widely in a number of diseases[137]. Normal values for children of several ages are listed in Table 2 which also illustrates the variability encountered[64,124]. These data show values for children of all ages to be high in comparison with those for adults but they do not show a significant sex difference or trend from one age to another among either infants or children.

TABLE 2.—FREE ERYTHROCYTE PROTOPORPHYRIN

(μg/100 cc. packed red cells)

NORMAL INFANTS, CHILDREN, AND ADULTS

	Hsia and Page[64]		*Sturgeon*[126]	*Watson*[143]
N	24	19	18	50
Range	46–203	22–175	18–155	24–52
Mean	86	66	50	36.4
S.D.	37	37	32	8.5
Age	0–5 days	3 weeks to 15 years	3–10 years	17–70 years

TABLE 3.—FREE ERYTHROCYTE COPROPORPHYRIN

(μg/100 cc. packed red cells)

NORMAL INFANTS, CHILDREN, AND ADULTS

	Schwartz and Wikoff[112]	*Hsia and Page*[64]		*Watson*[143]
N	2	24	19	50
Range	5.3–8.1	0.2–3.1	0.5–2.7	0–2.0
Mean		1.6	1.1	0.5
S.D.		0.7	0.57	0.54
Age	Cord blood	0–5 days	3 weeks to 15 years	17–70 years

Free coproporphyrin (type III isomer) was first isolated from normal human erythrocytes by Schwartz and Wikoff[112]. Watson's study of erythrocyte coproporphyrin levels in a variety of anemias indicates that these values provide an accurate index of erythropoietic activity since they parallel the reticulocyte count closely[143]. Table 3 compares the values reported for nor-

mal children of various ages with those found in adults[64,112,143]. Inspection of these data reveals that infants display significantly higher erythrocyte coproporphyrin concentrations than adults, but that the difference between the latter and normal children is probably not significant. The increase in newborns is probably best explained on the basis of accelerated erythropoiesis *in utero*.

Free erythrocyte uroporphyrin has not been demonstrated in normal subjects, but, in erythropoietic porphyria with severe hemolysis, uroporphyrin I can be crystallized from circulating red blood cells[1]. One might speculate that uroporphyrin will be detected there if erythrocyte porphyrins bear the same relationship to each other as urinary porphyrins.

Very likely, the free porphyrins occurring in normal erythrocytes represent residues remaining in the cell after hemoglobin synthesis is complete. This speculation seems justified in view of the alterations observed during disordered hemopoiesis.

Human Porphyrias. The classification and definition of human porphyrias have undergone significant changes in the past few years. It is now apparent that, so far as uroporphyrin excretion is concerned, the metabolic error is quantitative rather than qualitative and that the disease can be divided into two principal categories. These are 1) ERYTHROPOIETIC PORPHYRIA which stems from abnormal porphyrin or hemoglobin formation in the bone marrow[1,13,106,107], and 2) the HEPATIC PORPHYRIAS which show normal bone marrow findings but high concentrations of porphyrins and porphyrin precursors in the liver[106,145]. The syndrome of passive porphyria, which is limited to newborn infants, should be considered as a separate entity[70,155]. Despite the fact that all porphyrias are characterized by the excretion of large amounts of uroporphyrin, there are fundamental clinical and biochemical differences between them.

a) ERYTHROPOIETIC PORPHYRIA (congenital or photosensitive porphyria). Although this type of porphyria is rare, it has intrigued both physicians and chemists for a great many years. Much of the basic chemical knowledge of porphyrins has come from the meticulous studies of the celebrated patient, Petry[36,37,39], by Hans Fischer and coworkers. In this disease, the metabolic defect is occasionally familial and is located in the developing normoblasts of the bone marrow where the abnormal amounts of uroporphyrin I and coproporphyrin I permeating the tissues and appearing in high concentrations in the excreta are formed[13,107].

A hemolytic process is nearly always present in these patients which has led to the postulate that excessive generation of type I porphyrins reflects abnormally rapid hemoglobin synthesis stimulated by hemolysis[1,53,54,57,58,79,86,89,100,106,107]. Neither the defect in hemoglobin formation nor the nature of the hemolysis is understood, but erythrocyte survival studies suggest an intracorpuscular abnormality[100,107]. The spleen is nearly always enlarged and its role is equally mysterious. However, surgical removal has been followed by improvement in the hemolytic process[1,55,106,107] and, in turn, in the porphyria.

This disease is characterized by a very early onset; in fact, red urine may be noted on the diaper soon after birth. Exposure of the urine to a Woods (ultra-violet) light reveals the characteristic red fluorescence of porphyrins. Skin photosensitivity is a striking feature of the disease, with exposure to sunlight being followed by the formation of extensive bullous eruptions on the exposed surfaces. These lesions be-

come pustular and break, leaving shallow, slow-healing ulcers. If irradiation is repeated, extensive mutilation of the ears, nose, scalp and digits may ensue. Before antibiotics became available, infection of ulcerated skin lesions presented a serious complication, often aggravating the tissue destruction. Hypertrichosis resembling that of Cushing's syndrome along the hairline is common, but its mechanism is still unknown. The deciduous teeth are usually stained reddish brown by the deposition of porphyrins in the tooth substance. Although palpation of the abdomen may reveal splenomegaly, pallor need not be present if the hemolytic process is compensated by increased bone marrow activity. Reticulocytosis and high porphyrin concentrations are seen in the peripheral blood. Bone marrow aspirates show normoblastic hyperplasia, and fluorescence microscopy may disclose the presence of porphyrins in the normoblasts. This phenomenon is clearly pictured in recent papers by Schmid and Schwartz[106,107].

Chemical studies of the urine and feces show increased fecal urobilinogen during active hemolysis. Large amounts of uroporphyrin I and coproporphyrin I can be isolated from the excreta with the former predominating in urine and the latter in feces. A 4-year-old girl studied by one of us (RAA) excreted over 100 mg. of uroporphyrin and 13½ mg. of coproporphyrin in 24 hours[1]. Both uroporphyrin and coproporphyrin can be isolated from the plasma, and erythrocyte and bone marrow porphyrins are also greatly elevated[106,107]. The usual laboratory tests for liver function give no evidence of liver damage and no evidence of renal dysfunction has been demonstrated. Porphobilinogen is not encountered in this form of the disease, and the porphyrins in the excreta are in the free state, in contrast to their appearance as zinc complexes in hepatic porphyria.

Management of erythropoietic porphyria is directed at preventing the effects of photosensitivity and controlling hemolysis. Protective ointments are generally unsatisfactory and the child must learn to live within a shaded area and to use proper clothing. Even brief exposure to direct sunlight is sufficient to provoke severe skin damage. Hemolysis can be partially arrested by splenectomy in some instances. In four cases treated in this way, reduced blood and urinary porphyrin concentrations coincided with relief of photosensitivity and hematologic evidence of decreased hemolysis. Although it may give only temporary improvement, splenectomy deserves careful consideration as a therapeutic measure in every such case because of its dual effect on photosensitivity and the hemolytic process[1,107].

The prognosis is good if a proper program of management is initiated early in childhood so that the individual learns to live with the disease.

HEPATIC PORPHYRIA. 1) *Intermittent acute.* This variety is uncommon in children before puberty and is rarely included in the differential diagnosis of abdominal colic or ascending paralysis in this age group. The disorder is familial, probably inherited as a Mendelian dominant characteristic with poor penetrance. With few exceptions, the cases reported in the medical literature have presented their initial symptoms after adolescence, although Kark states, in his fine discussion of the porphyrinopathies, that many patients gave histories of mild symptoms from childhood or early adolescence[68]. Clinical and urinary examinations of all relatives of known porphyrics would undoubtedly disclose additional subclinical cases[19,69]. Such studies might also uncover additional children with very

mild clinical or chemical manifestations in time to avoid exposure to agents known to precipitate severe attacks. No single physician has seen a sufficient number of children having hepatic porphyria to enable him to state clinical and chemical criteria paralleling those already defined for adults[16,61,68,99,106,131,135,147,148].

In hepatic porphyria, as the name implies, the derangement in porphyrin metabolism apparently resides chiefly in the liver[106], where the enzyme, catalase, has been implicated[103]. The bone marrow is normal in hepatic porphyria, and isotopic studies of porphyrin and hemoglobin metabolism in one such case not only showed a normal erythrocyte life span but also suggested that some of the excessive fecal porphyrin formation also occurs in the central nervous system, the kidney, and other tissues.

The clinical and chemical features of human porphyria are compiled in Table 4. Most of the signs and symptoms listed are characteristic of adults. In the few examples of this disease reported in children the principal presenting symptoms were abdominal colic with pain and weakness of the lower extremities[5,9,26,32,40,81,87,101]. Death, when it occurred, was the result of a rapidly ascending paralysis that finally involved the medullary centers. One child, a patient of Dr. Harriet Guild, presented nearly all of the adult features including abdominal pain, hypertension, convulsions, vomiting, constipation, and severe polyneuritis[40].

Apparently the abdominal pain suffered by porphyric patients is excruciating, since individuals who have undergone other extremely painful experiences invariably describe porphyric colic in the strongest terms. Despite the severe discomfort, there is little or no abdominal tenderness and splinting is generally not present. Pain may radiate into either flank or downward and, when accompanied by dark urine, suggests renal stones. The cramps are probably spasms of the intestine and often occur concomitantly with abdominal distention and obstipation[20]. Because of the location and character of the pain, many of these people have undergone exploratory laparotomy on one or more occasions. These laparotomies reveal no significant lesion and do not relieve the symptoms. All clinicians, surgeons in particular, should beware of the patient with "neurotic" manifestations who has been previously explored for abdominal pain. An unnecessary operative procedure may be avoided if porphobilinogen, which is pathognomonic of hepatic porphyria, is identified in the urine[136]. Abdominal pain is common in childhood and it may be that intermittent acute porphyria will be recognized more frequently in children when this simple urine test is widely applied.

Paralysis or weakness associated with colic facilitates recognition of porphyria. Typically, pain starts in the lower extremities and arms, followed by paresthesias, weakness, and loss of deep reflexes and sensation. The findings resemble those of a slowly ascending polyneuritis which may involve the medullary centers causing bulbar paralysis. This symptom complex is sufficiently reminiscent of poliomyelitis that some porphyrias have been so diagnosed before the true nature of the disease was established. Changes in the cerebrospinal fluid and stiffness of the neck and back are not seen in porphyria and, once more, the urinary porphobilinogen test is diagnostic. Lead poisoning, diphtheria, and the progressive degenerative diseases of the central nervous system seen in children do not show strongly positive porphobilinogen tests or large amounts of urinary uroporphyrin.

TABLE 4.—CLINICAL AND CHEMICAL FEATURES OF HUMAN PORPHYRIA

		Hepatic		
	Erythropoietic	*Intermittent Acute*	*Chronic Cutaneous*	*Passive*
Onset	Infancy or childhood	Young adults	Middle-aged adults	Newborn
How transmitted	Mendelian recessive	Mendelian dominant (poor penetrance)	Mendelian dominant (poor penetrance)	Transplacental
Clinical	Skin photosensitivity Red urine Erythrodontia Hirsutism Splenomegaly Hemolytic anemia	Abdominal colic Weakness or paralysis Pain in arms or legs Psychosis Hypertension Obstipation Oliguria Coma	Skin photosensitivity Violaceous hue Pigmentation Liver cirrhosis Skin thickened and scarred	No signs or symptoms
Marrow porphyrins	Greatly elevated	Normal	Normal	
Blood porphyrins	Uroporphyrin I Copro-I in rbc and plasma	Normal	Uroporphyrin and coproporphyrin detectable in plasma	
Urine	Red color and fluorescence Uroporphyrin I and copro-I (zinc complex and porphobilinogen absent)	Zinc complex of uroporphyrins I and III and copro-III Porphobilinogen present Darkens on standing	Zinc complex of uroporphyrins I and III and copro-III Porphobilinogen absent Orange or red color	Contains same porphyrins and precursors as found in mother
Liver porphyrins	Slight elevation	Elevated, especially porphyrin precursors	Elevated, mostly porphyrins	
Prognosis	Good	Fair, poor after recurrences	Good depending on liver status	Excellent
Treatment	Protect skin Splenectomy	Symptomatic, avoid alcohol, barbiturates and hepatotoxins. ACTH or cortisone (?)	Symptomatic, avoid hepatotoxins, sedatives, alcohol protect skin	None

Hypertension is common in acute attacks of hepatic porphyria, usually appearing when paralysis is marked. Kezdi has investigated the mechanism of this rise in blood pressure and concluded that it is not a direct "toxic" effect of porphyrins or porphobilinogen, but probably results from malfunction of the inhibitory carotid sinus nerves[71]. He further implied that the presence of pathologic changes in the reticular formation may mean that the hypertension of porphyria is functionally similar to that of bulbar poliomyelitis[6,60].

Psychosis, when it occurs, usually precedes coma and death. Hallucinations are common when central nervous system involvement is severe. However, the clinician is often amazed at the rapidity with which patients recover from an apparently very deep psychotic state.

The biochemical defects responsible for the signs and symptoms of intermittent acute porphyria remain to be elucidated. The symptomatology cannot be explained on the basis of circulating porphyrins alone since the high plasma porphyrin concentrations seen in erythropoietic porphyria are never accompanied by abdominal colic or neurologic disturbances. Furthermore, patients suffering from another type of hepatic porphyria, the chronic cutaneous type, characteristically do not present abdominal or central nervous system manifestations unless porphobilinogen appears in the urine. What then is the role of porphobilinogen in relation to these signs and symptoms? Some investigators have felt that porphobilinogen may be "toxic," but exhaustive pharmacologic studies of the effects of porphobilinogen and porphyrins on animals have led to the conclusion that neither porphobilinogen nor free porphyrins exert any significant pharmacological action[46]. In addition, porphobilinogen administered enterally to rats is rapidly excreted in the feces; when given parenterally, it is quickly eliminated in the urine[48]. This rapid excretion, coupled with the observation that porphobilinogen does not accumulate in the liver when given by either route, suggests that the porphobilinogen found in the liver in hepatic porphyria is formed *in situ*. When delta-aminolevulinic acid, the immediate precursor of porphobilinogen, was administered orally to a normal adult with the exception of a transient photosensitivity, no signs or symptoms of porphyria were observed[10]. Labeled delta-aminolevulinic acid administered to two patients with intermittent acute porphyria was converted to urinary porphobilinogen to a much greater degree than in the normal subject[91]. Granick has recently reported the urinary excretion of rather large quantities of delta-aminolevulinic acid by a patient with intermittent acute porphyria during a clinical remission[52]. These observations suggest that delta-aminolevulinic acid, like porphobilinogen and porphyrins, is not "toxic" for normal or porphyric human beings. Administration of delta-aminolevulinic acid to normal rats has yielded evidence that it is converted to porphobilinogen and porphyrins by these animals without demonstrable toxic manifestations[10,52]. Finally, no clinical evidence of porphyria has been observed in the newborn offspring of porphyric patients, although, in each instance, diffusion of porphyrins across the placental membrane was clearly indicated[70,155]. Surely, if the porphyrins or their precursors are injurious to human tissues, their deleterious effect should be manifested under these conditions which combine rapidly growing embryonic tissue, presumably highly sensitive to "toxic" agents, with constant exposure

to the supposed "toxin" over a period of several months.

The available evidence, therefore, suggests that the signs and symptoms of intermittent acute porphyria, as well as the occurrence of porphyrins and their precursors in tissue, result from an underlying disorder in cellular metabolism involving other biochemical entities. This concept will be developed more fully in the section on experimental porphyria.

2) *Chronic cutaneous porphyria* (cutanea tarda). Chronic cutaneous porphyria is also familial, usually runs a mild course, and has a fairly good prognosis. Excellent descriptions of the disease as it appears in middle-aged adults are quite numerous[15,16,19,82,106,147,152]. In the tabulation of cases observed by the University of Minnesota group, only one, Case 119, was listed as starting in childhood[106]. Clinically, the disorder is characterized by the occurrence of skin photosensitivity and pigmentation with development of cirrhosis of the liver late in the course of the disease. Table 4 compares its signs, symptoms and chemical characteristics with those seen in intermittent acute porphyria. Chemically, the principal difference between these disorders lies in the absence of porphobilinogen from the urine in the chronic cutaneous type. Otherwise, the porphyrin excretions are very much alike. Since chronic cutaneous porphyria differs from the other variety of photosensitive porphyria in that the metabolic anomaly lies in the liver rather than in the bone marrow, there is little rationale for splenectomy in these patients. Their management should be directed toward avoidance of hepatotoxins of all sorts as well as minimal exposure to sunlight.

3) *Mixed porphyria.* The term mixed porphyria is reserved for patients presenting abdominal or nervous symptoms, or both, in association with porphobilinogenuria during the course of chronic cutaneous porphyria. The clinical and chemical picture resembles both of the preceding forms of hepatic porphyria (Table 4). Occasionally, abdominal and nervous symptoms occur when photosensitivity is in remission[106] suggesting a close relationship between these clinical forms of hepatic porphyria. Furthermore, cases of both chronic cutaneous and intermittent acute porphyria may occur in the families of patients having mixed porphyria[15,16,19,106,152].

The isomeric configuration of the uroporphyrins excreted by patients suffering from the various types of hepatic porphyria has long been a subject of disagreement. It now appears that differences in the techniques employed by various investigators may account for their contradictory results. Recent studies indicate that both uroporphyrin I and a type III porphyrin having solubility characteristics similar to those of the uroporphyrins are present. Several complete reviews of this subject have been published[34,35,149,150].

c) PASSIVE PORPHYRIA. Two infants born while their mothers were suffering clinical attacks of porphyria (one mother had erythropoietic and the other intermittent acute porphyria)[70,155] have been studied. Although the babies excreted porphyrins and porphyrin precursors during the first days of life, they failed to show any other signs or symptoms of porphyria. The porphyrins and their precursors disappeared from the babies' excreta within a few days indicating that the children were not afflicted with porphyria.

The baby whose mother (previously reported by Ashby)[4] suffered from classical erythropoietic porphyria was a normal appearing male[70]. At birth his erythrocytes contained both uroporphyrin I and coproporphyrin I. Only coproporphyrin was noted in the

plasma. The meconium contained 9.65 mg. of porphyrin, which proved, on chromatographic separation, to be a mixture of uroporphyrin, coproporphyrin and some unidentified di- and tricarboxylic porphyrins. Unfortunately, the urine was not examined during this first day of life but during the second day 140 mcg. of coporporphyrin were excreted. Subsequent examinations of blood and excreta were negative. Since both the maternal porphyrins and those obtained from the infant were type I isomers, it is probable that those found in the baby were derived from the mother, either through the entry of maternal erythrocytes into the fetal circulation, or by diffusion of the porphyrins in the maternal serum across the placental membrane. Porphyrins were not demonstrable in the mother's milk, suggesting that the secretory alveoli are impermeable to porphyrins.

The other infant was a premature Negro female born while her mother was suffering a severe attack of intermittent acute porphyria[155]. The baby responded well to supportive measures and survived but the mother expired 8 days postpartum. On the first day of life the baby's urine was the color of port wine, showed a trace of porphobilinogen, 100 mcg./100 cc. of uroporphyrin, and 400 mcg. of coproporphyrin, predominantly type III. Later specimens were amber colored and uroporphyrin was not demonstrable. Urinary coproporphyrin concentrations declined rapidly, falling to 51.5 mcg. on the second day and 1.5 mcg. at 10 weeks of age. Since normal values for urinary coproporphyrin at this age have not been reported, these later figures are difficult to interpret.

Subsequent clinical observations revealed that, although the child's motor function developed normally, her teeth were not discolored, and she displayed no other signs of hepatic porphyria, her stature and weight were sufficiently small to suggest true primordial dwarfing. Little is known about the effects of porphyria on growth mechanisms and one can only speculate about the relationship suggested. However, it should be mentioned that chick embryos with experimental porphyria show distinct growth inhibition[128] and appear to form purines at a reduced rate[75,76].

Further studies of this type are desirable and should include continued observations on the growth and development of these children. Much valuable information could be contributed by long term study of the offspring of porphyric patients.

Experimental Porphyria. Progress toward a better understanding of the porphyrias has been hampered by the serious limitations inherent in studies utilizing human subjects as well as by the rarity of the diseases. Spontaneous porphyria has been described in cattle and pigs[22,41,42,43,97,99] but these examples are limited to a variety corresponding closely to erythropoietic porphyria in human beings. Interest in this disease has been revived recently by a report of one bullock who excretes tremendous amounts of porphobilinogen in the urine[65]. The fox squirrel suffers from a "physiological" porphyria resembling the hepatic type of human porphyria. This animal has been studied quite extensively[130] but is not suitable for controlled laboratory experiments because it is so difficult to handle. Thus, the practical difficulties involved in dealing with farm animals and the wild fox squirrel has limited their usefulness. Accordingly the development of a suitable experimental method for producing porphyria in laboratory animals has been keenly anticipated by both chemists and clinicians.

Porphyria has been produced experimentally in rabbits, rats and chickens[21,

TABLE 5.—EXPERIMENTAL PORPHYRIA

		Rabbit		*Rat*		*Chick Embryo*
	How produced	Lead, phenylhydrazine, Rose Bengal, sunlight	Allylisopropylacetylcarbamide	Allylisopropylacetylcarbamide	Allylisopropylacetamide	Allylisopropylacetylcarbamide
	Bone marrow Porphyrins	Elevated Uroporphyrin I Coproporphyrin III	Normal	Not quantitated No fluorescence	Not quantitated	Not quantitated No fluorescence
	Liver Porphyrins	Normal	High uro-, copro- and proto-	High uro-, copro- and proto-	High uro-, copro- and proto-	Elevated
	Liver Catalase		Activity reduced	Activity low	Activity low	Activity low
U	Uro type	I	Mainly III	Mainly III	Mainly III	Mainly III
R	Copro type	III	Mainly III	Mainly III	Mainly III	90% III
I	Porphobilinogen	Present	Present	Present	Present	Present
N	Zinc complex	10%	Up to 80%	Predominant	Predominant	
E	Free porphyrin	90%	20% or more	Small amount	Small amount	
C	Weakness	Rarely	Usual	Usual	Usual	Common
L	Lethargy	Absent	Usual	Usual	Mild	Not seen
I	Anorexia	Absent	Usual	Usual	Present	Not seen
N I C A L	Intestinal distention	Absent	Usual	Present	Mild	Not seen
	Paralysis	Absent	Frequent	Common	Occasional	Observed in some after hatching
	Comment	Urobilinogenuria suggests liver damage	Prompt recovery when drug stopped	High mortality	Less mortality	Growth inhibition and malformations noted
	References	104, 114	49, 105	21	49	2, 128

[49,104,105,114,128] and the methods used, as well as the principal chemical and clinical features of the disease in each species, are shown in Table 5. In rabbits, the use of lead, phenylhydrazine, Rose Bengal dye, and sunlight produces a porphyria resembling the human erythropoietic form most nearly but also having some of the features of hepatic porphyria. On the other hand, treatment of rabbits, rats or chickens with allylisopropylacetylcarbamide (Sedormid), or its close relative allylisopropylacetamide, produces an experimental porphyria closely akin to the intermittent acute porphyria of man. Chemically, this experimentally induced porphyria is almost identical with that seen in human beings and shows some clinical similarities in the form of weakness, paralysis, dilatation of the gastrointestinal tract, and anorexia. Furthermore, porphyrins and porphyrin precursors are similarly distributed in the tissues. The bone marrow shows no evidence of porphyrin accumulation but the liver is extremely rich in porphyrin precursors, and, to a lesser extent, preformed porphyrins.

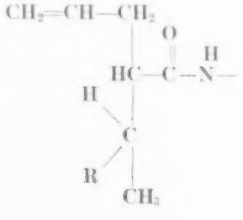
In experimental animals, liver catalase activity falls to very low levels following treatment with allylisopropylacetylcarbamide or allylisopropylacetamide. This change in enzyme activity is under intensive investigation[106]. Reduced liver catalase activity may be explained by increased destruction of the enzyme, inhibition of enzyme activity, or impaired enzyme synthesis. The simultaneous occurrence of very large amounts of porphyrins and porphyrin precursors in hepatic cells and markedly reduced liver catalase activity supports the latter explanation. The rate at which liver catalase activity diminishes following treatment with porphyria-producing drugs (24 to 48 hours) suggests that if the drug affects the biosynthesis of the enzyme, its half-life must be rather short. On the other hand, the length of time required for liver catalase activity to be greatly reduced argues against its reduction as a result of inhibition. Should it be found that the catalase turnover rate is very rapid, the evidence in favor of impaired synthesis would be strengthened.

Studies utilizing porphyric chick embryos have yielded evidence that purine metabolism also is deranged in experimental porphyria. That is, in porphyric embryos, a *reduction* in uric acid excretion correlating well with the *increase* in porphyrin excretion has been observed[75]. Exogenous adenine is not only oxidized and excreted normally by these embryos, but it also induces a significant reduction in their porphyrin outputs. Furthermore, after intravenous alpha-C^{14} glycine, much less label appears in the uric acid excreted by porphyric embryos than in that excreted by control embryos[76]. A plausible explanation for simultaneous disturbances in purine and porphyrin metabolism is provided by the recent work of Shemin and associates[121,123,124,156] showing that the biosyntheses of these two classes of compounds involve a common intermediate, delta-aminolevulinic acid. Inspection of the succinate-glycine cycle postulated by Shemin even reveals a probable site for the biochemical lesion in porphyria. That is, if this cycle were blocked at the point where delta-aminolevulinic acid undergoes oxidative deamination to give alpha-ketoglutaraldehyde, a deficiency in the one carbon fragments required for purine synthesis would ensue, and delta-aminolevulinic acid would accumulate, thus accelerating porphyrin formation on a mass action basis[75].

Chick embryos with experimental porphyria grow at a reduced rate and this effect persists for at least 30 days

after hatching[128]. Other anomalies noted in porphyric embryos include "clubbed down," cysts over the caudal region, and a flaccid condition of the legs and feet with the toes distorted. After hatching, many of these chicks still exhibited curled toes in addition to symptoms of neurological involvement such as paresis, tremors, and weakness[2]. Although the exact cause of these abnormalities is not yet known, their appearance is not surprising in view of the fact that two major pathways of metabolism (porphyrins and purines) are seriously altered in this disorder.

From the foregoing discussion it is clear that the use of appropriate drugs opens the way to intensive metabolic studies in porphyria. Studies of the biochemorphology of porphyria-producing drugs may aid materially in identifying the enzyme system(s) involved and lead to an effective treatment for this disorder. Several studies of this type have been reported recently[47,49,129,151] and the chemical structure required to produce porphyria is now fairly well defined. This structure is diagrammed below:



Porphyrinurias. The term "porphyrinuria" designates an increase in the amount of urinary porphyrins without regard to the kind of porphyrin present. This definition permits porphyria to be classed as a porphyrinuria, but, in common usage, the term porphyria is applied only to those individuals excreting *excessive* amounts of uroporphyrin.

a) LEAD POISONING. Coproporphyrinuria, with the porphyrin predominantly the type III isomer, is a constant finding in lead poisoning[7,8,59]. This subject has been reviewed by several authors[23,133,138,151]. In children, the principal danger of lead poisoning lies in the permanent cerebral damage which may follow intoxication[17,18]. It is interesting to recall that central nervous system changes also constitute a hazard in attacks of intermittent acute porphyria. Urinary coproporphyrin excretion has been utilized in industry to detect cases of incipient lead poisoning, since the porphyrinuria precedes overt clinical manifestations by several weeks. When lead poisoning is treated with calcium versenate, the porphyrin excretion rapidly falls to normal levels[8]. Thus, the quantitative determination of urinary coproporphyrin not only aids in diagnosis, but also serves as a useful index of adequate therapy.

A number of years ago, Rimington advanced the hypothesis that lead interfered with the enzymatic combination of iron, protoporphyrin, and globin during the synthesis of hemoglobin[98]. Later work has demonstrated that erythrocyte coproporphyrin values are only slightly elevated in lead intoxication and that the urine of these patients contains increased amounts of uroporphyrin and occasionally contains porphobilinogen[7,8,113]. Furthermore, Eriksen's *in vitro* studies of heme synthesis[31] indicate that lead affects porphyrin biosynthesis rather than the incorporation of iron into protoporphyrin. Since porphyrins are known to be synthesized in tissues other than the bone marrow, such an effect of lead offers a better explanation for the widespread symptoms of lead poisoning.

b) RHEUMATIC FEVER. Coproporphyrinuria is a consistent finding in children with acute rheumatic fever[92]. The

type III isomer predominates, as previously reported by Kapp and Coburn[67]. Quantitatively, this coproporphyrinuria parallels the serum mucoprotein levels and the clinical course of the illness. In affected children, free erythrocyte porphyrin levels lay within the normal range indicating that abnormal hemoglobin formation does not offer a suitable explanation for this coproporphyrinuria[92]. Since the liver appears to be the site of the marked alterations in porphyrin metabolism seen in hepatic porphyria, it follows that the extra coproporphyrin excreted in rheumatic fever may arise in the liver or other parenchymal organs.

Limited experience with children suffering from other collagenous diseases, disseminated lupus erythematosus, rheumatoid arthritis, and polyarteritis nodosa, indicates that coproporphyrinuria occurs in these diseases also. Pursuit of this lead may aid in elucidating the pathologic physiology of these poorly understood entities.

c) POLIOMYELITIS. The occurrence of coproporphyrinuria in this virus disease presents another example of porphyrinuria associated with damage to the central nervous system[139]. This coproporphyrinuria contrasts with that seen in viral infections of the liver in that the porphyrin excreted by poliomyelitis patients is the type III isomer, while that excreted by patients with liver disease is mainly type I[141]. It is interesting to speculate that, in poliomyelitis, the urinary coproporphyrin may be derived from the central nervous system[66,73,74]. Correlation between urinary coproporphyrin values and the outcome of the disease was poor. Similarly, there was no clear relationship between the degree of paralysis and the coproporphyrinuria, suggesting that the porphyrin was probably not derived from myoglobin.

d) LIVER DISEASE. Infectious hepatitis, a virus disease, results in the increased urinary excretion of coproporphyrin, type I[141]. Alcoholic cirrhosis, on the other hand, produces a coproporphyrinuria in which the type III isomer predominates, and even normal individuals develop a transient coproporphyrinuria (type III coproporphyrin) following the ingestion of varying amounts of alcohol[127,146]. The possibility that some of the coproporphyrin excreted under these circumstances may arise in the central nervous system cannot be excluded, but it seems more likely that alcohol may affect porphyrin formation in liver cells to produce this effect.

e) ANEMIAS. Coproporphyrinuria is seen in pernicious anemia and the hemolytic anemias, the coproporphyrin being the type I isomer[27,99,138]. Aplastic anemias attributable to poisoning of the bone marrow may display increased urinary coproporphyrin of either isomer type[138,147]. In the anemias associated with accelerated erythropoiesis, the type I coproporphyrin eliminated in the urine is believed to arise in the bone marrow as a by-product of hemoglobin synthesis. The source of the extra coproporphyrin III excreted in other types of anemia remains to be established. It may be either the liver or the bone marrow. Iron deficiency anemia characteristically is associated with increased erythrocyte protoporphyrin and urinary coproporphyrin (type III). The porphyrin appearing in the urine in this condition probably comes from the bone marrow.

f) IDIOPATHIC COPROPORPHYRINURIA. Occasional individuals exhibit a physiological coproporphyrinuria, the porphyrin being the type III isomer. These individuals are asymptomatic and do not give histories or signs of exposure to infection, chemical poisons, or other agents leading to coproporphyrinuria[113].

Since uroporphyrin and porphobilinogen were absent from the urine, these people probably are not afflicted with porphyria[142]. All such individuals reported thus far are adults and no other examples have been found in their families. Identification of this metabolic anomaly provides further evidence that the porphyrins themselves are not toxic.

g) RADIATION. Koch and his associates[72] have reported coproporphyrinuria in patients receiving therapeutic doses of I^{131}. The isomeric configuration of the porphyrin was not stated, but the authors discuss the possible sources of the coproporphyrin.

Summary. The chemistry and metabolism of porphyrins have been reviewed with particular emphasis upon alterations in porphyrin metabolism in childhood. It is now apparent that the metabolic error characteristic of porphyria must be considered as a quantitative rather than a qualitative one. There are also indications that the porphyrinurias reflect a more profound disturbance in cellular metabolism than previously believed. The fundamental investigations utilizing animals suffering from drug-induced porphyria as well as the *in vitro* techniques which have led to this new information are discussed.

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SUMMARIO IN INTERLINGUA

(See page 605 for original article)

Sanitate Public, Fertilitate, e Economia General in lor Effectos Combinate Super le Standard del Vita

III. Evalutation Quantitative del Componentes Determinante con Reguardo al Question del Elevar o Mantener le Standards nunc Existente

Per medio de 6 procedimentos analytic nos ha calculate e estimate le requirimentos que debe esser satisfacite pro promover o mantener le nivellos del existentia in paises e territorios con differente grados de disveloppamento, specialmente in paises e territorios de pauc disveloppamento al tempore presente. Esseva considerate primarimente objectivos theoric de definition specific. Per medio de illos, objectivos plus realistic esseva derivate.

Nostre constatationes indica que le densitate del population e le rapiditate de su augmentation in multe paises de basse disveloppamento economic ha jam attingite si alte nivellos que omne essayo a altiar le standard del vita a solmente un rango intermediari in le presente scala general es practicamente inattingibile si un tal essayo es interprendite exclusivemente per medio de meliorationes agricultural e industrial. In plus nostre datos indica que le controls de morbos, non accompaniate per le propagation de ideas educative in re le problemas del fertilitate, servi solmente a render le situation plus grave, proque assi le controlo de morbos tenderea a neutralisar le signification de altere avantiamentos.

Le analyse del disponibile mechanismos operative demonstrava que programmas de hygiene es especialmente significative, proque illos exerce un influentia super natalitate e mortalitate e proque istos, de lor parte, affice le nivello del existentia secundo functiones potentiate, durante que altere mechanismos exerce un influentia super factores que produce lor effectos secundo functiones normal.

Il deveniva clar que programmas de hygiene pote esser usate pro rumper le existente tyrannia de indifferentia e apathia e etiam pro assecurar que le meliorationes effectuate se establi como factos permanente.

Nos conclude que emphase special es a prestar a cautemente planate e ben balanciate programmas de hygiene como base initial pro le promotion de altere interprisas meliorative e que investimentos in hygiene durante le prime phases va provar se profitabile con un plus alte grado de probabilitate que equivalente investimentos in altere programmas.

GYNECOLOGY AND OBSTETRICS

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A FIVE-YEAR SURVEY OF THE LITERATURE IN CANCER OF THE CERVIX

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DURING the past 5 years there has been an increase in the reported incidence of cervical cancer and a concomitant decrease in mortality from cancer of the cervix[69]. Although it is encouraging that there has been an improvement in survival rates, it is obvious that the absolute cure rate will not be appreciably increased except by earlier diagnosis of such lesions. To this purpose every known approach is being investigated. Etiological factors have been studied, diagnostic methods devised and perfected, and radiotherapeutic and surgical techniques improved to facilitate early diagnosis and subsequent cure.

Etiology. Cervical carcinoma is the second most common cancer in American women[78] and accounts for approximately 10% of all newly diagnosed cases and for about 10% of all cancer deaths. In different American cities the annual incidence varies from 30 to 60 per 100,000 females[111]. Extensive studies have been made of the racial and geographic distribution of cervical cancer in order to elucidate possible etiological causes. Conditions that have been investigated are the factors of age and marital status, circumcision, low economic status, cervicitis and infection, hormones, and the influence of heredity[10,13,20,35,36,48,61,70,78,82,102,111].

Age may be a factor in the incidence of cervical cancer, since the disease occurs only occasionally in younger patients, and is rare in women less than 35 years of age and in those over 70[103]. It has long been known that cervical cancer is rare among single women; however, numerous studies have shown that the number of pregnancies is not an important predisposing factor, whereas the age of first coitus and child-bearing seem significant[69,70]. Such conditions as the onset and regularity of menses, number of miscarriages and abortions, use of contraceptives, irritative vaginal discharge, and frequency of douching evidently have no direct bearing on the development of cervical cancer[99,111].

In the United States, about 2.28% of women over 20 develop cancer of the cervix[89]. The incidence among Jewish

women is one-fifth to one-tenth that in non-Jewish women, whereas in Israel, the cancer rate is even lower[17,84,95,99,109,111]. It has been suggested that a possible cause of this low incidence of cervical cancer is the Jewish practice of abstinence from sexual intercourse during most of the first half of the ovulatory cycle[13,109]. The fact that carcinoma of the cervix is relatively rare among Jewish women and that penile cancer is almost unknown among circumcised males suggests a causative relationship of smegma and carcinoma of the cervix[13,109]. Demographic studies seem to support this theory, although it has not been proved[102]. For example in India the frequency of cervical cancer among Moslems who practice circumcision is only about two-fifths that of the Decanni Hindus who do not practice circumcision[61,100,109,111]. In experiments with mice, paste made from smegma was applied to the cervico-vaginal area. These applications produced epithelial hyperplasia of the mucosa. The investigators concluded that the bacterial action in decomposing smegma might transform the cholesterol content into a carcinogenic agent[88].

Since epidermoid cancer of the cervix has been found in virgins and in patients who have not had coition with noncircumcised males, etiologic factors besides lack of circumcision must therefore exist[111]. Investigation among different groups has shown that in populations with a high incidence of cervical cancer there is also poor penile hygiene. It should be remembered, however, that, in the words of one investigator, "any patient with a cervix may develop a carcinoma"[95]. In general, then, it has been concluded that population groups in which there is customarily first coitus at a comparatively late age and in which circumcision is practiced have the lowest rate of cervical cancer.

Cancer of the cervix is more common among colored populations than among white[57,99,111]. For example, in the Bantus of South Africa, cancer of the cervix accounts for 54% of all cancer, and among American Negroes, cervical cancer is 60% more frequent than it is among whites[100,111]. Although there may be some racial predisposition, it has been suggested that low economic status with such coexisting conditions as poor obstetrical care, improper housing, and inadequate nutrition may have some etiological significance[20,38,100].

Cervicitis is so common among married women that it has been considered as a possibly precancerous lesion. Gagnon has stated that in over 3000 cases treated for chronic cervicitis no instance of cervical carcinoma subsequently developed. Also, relatively few cases of cervicitis and no cervical cancer were found among 15,000 nuns surveyed in Canada[35,36,70]. The rarity of cervicitis alone would not account for the low incidence of cervical cancer among Jewish women, since chronic cervicitis is frequent in this group.

The incidence of syphilis and cervical cancer is twice that of cervical cancer alone in the general population. The statistical association between syphilis and cervical cancer could be accounted for on the basis of earlier age at first coitus and greater frequency of coitus among cervical cancer patients with syphilis[111]. For example, in a study in Denmark made by Rojel, cancer of the cervix was four times more frequent in prostitutes than in control groups of comparable economic status[93].

As regards the hormonal factor, animal experimentation has shown that estrogen administration increases the

incidence of cervical cancer in mice[13, 111]. Estrogen may exert a growth stimulating effect, since significant numbers of cancer patients show evidence of excessive tissue estrogen on the basis of vaginal and cervical cornification[111]. In 200 cases of invasive and preinvasic carcinoma, Nieburgs found the commonly associated complaints were those of estrogen deficiency rather than increased estrogen activity[81,82]. In contradistinction, the equal incidence of cervical cancer in different age groups suggests that cancer development is not necessarily dependent upon the normal decline of estrogen activity after the menopause. Instead, 70% of postmenopausal women with preinvasive cancer fail to show the low estrogenic levels expected for that age group[81].

Some investigators believe that the low incidence of cervical cancer in Jewish women is a result of a genetic immunity and the theory has been advanced that this ethnic group may have a "special hormonal status"[70,71]. Despite numerous studies on the heredity factors, cervical cancer yet appears to be determined essentially by exogenous factors[13].

Only recently have the psychological aspects of pathogenesis of cervical cancer patients been investigated. In a study of the personality patterns in cervical cancer patients and breast cancer patients, Tarlau and Smalheiser found an apparent relationship between sexual difficulties and cancer of the cervix[101]. These findings were corroborated by Stephenson and Grace in a survey of 100 patients with cervical cancer, correlated with 100 patients with cancer in other sites[99]. The cervical cancer patients showed poor sexual adjustment and poor marital adjustment. Dislike and aversion for sexual intercourse were more frequent among cervical cancer patients than in patients with cancer in other sites, and these attitudes antedated the onset of the neoplastic disease by many years.[99,101].

Diagnosis. In order to facilitate early diagnosis of cervical cancer, the following international classification of the stages of carcinoma was adopted by the International Congress on Obstetrics and Gynecology in 1950:

Stage 0. Carcinoma *in situ;* also called "preinvasive" and "intraepithelial" carcinoma.

Stage I. Invasive carcinoma confined to the cervix.

Stage II. The carcinoma extends beyond the cervix but does not reach the pelvic wall; involves the vagina but not the lower third.

Stage III. The lesion involves the pelvic wall. On rectal examination no "cancer-free" space is found between the tumor and the pelvic wall.

Stage IV. The carcinoma involves the bladder or the rectum, or both, or extends beyond the limits previously described[53,63].

The agreement on the classification of carcinoma of the cervix represents an important advance in the diagnosis of cervical cancer. Although many authorities believe the classification is inadequate[15,75,78], it has afforded uniformity which is necessary in order to correlate therapeutic statistics from different investigators. Before the concept of "carcinoma *in situ*" was developed, cervical cancer was regarded as an invasive disease and an irreversible one[103]. Now, it is established that early intraepithelial, or preinvasive stages may exist for years before the lesion either *invades* or *reverts* to normal[3,74]. Obviously, it is impossible to predict which development will result.

In some cases, changes referred to as atypical hyperplasia, when limited in extent, are readily distinguished from carcinoma *in situ*[91]. When such changes are marked, the differential diagnosis is difficult[83]. Hence, many investigators believe that at least in some instances atypical hyperplasia antedates the development of frank cancer[91].

The cells of an intraepithelial lesion have much the same microscopic appearance as those of invasive cancer[34,63,66,74]. The hyperplastic changes involve the epithelium and the basal cell layer frequently shows hyperactivity[83]. The changes may involve the cervical glands, and glandular involvement is regarded by some authorities as evidence of stromal infiltration[58,63]. In many instances invasive carcinoma has been found in surgical specimens in cases in which preoperative biopsy showed only intraepithelial lesions[37]. Also, invasive cancer has developed many years after the initial biopsy showed noninvasive cervical carcinoma[28,34,37,51,74]. Undoubtedly all intraepithelial lesions do not progress to invasive cancer[37,110]. If, however, an intraepithelial lesion is not recognized as a preinvasive stage in the pathogenesis of invasive cancer in at least some instances, then there is, obviously, less reason for detection of carcinoma *in situ*[3]. The practice of examining asymptomatic women to detect carcinoma *in situ* loses significance unless this lesion is regarded as potentially invasive[74] and treatment instituted accordingly[37].

The average age of patients with carcinoma *in situ* is about 10 years less than that of patients with invasive cancer, the average age varying from 38.7 to 46.9 years. The greatest number of cases of carcinoma *in situ* occur at about age 40[34,51,69,74,91,110]. The incidence of carcinoma *in situ* has been variously reported as 0.84 to 3.9%[6,46,47,51,58,74,91].

Carcinoma *in situ* often occurs at the edge of an invasive carcinoma[51,74]. Hence, in cases in which a biopsy shows an intraepithelial lesion, the diagnosis should remain tentative[83] until multiple biopsies and curettage prove that the lesion is, in fact, only carcinoma *in situ* and that invasion of the stroma has not occurred[31,51,58,74].

If cervical carcinoma is diagnosed early, the cure rate should approximate 100%[28,37,103]. Actually, the 5-year survival rate throughout the world is only between 30 and 40%[28,52-55,103]. Early carcinoma produced no signs or symptoms, necessarily; therefore, frequent examination of apparently normal women is necessary in order to detect cervical cancer in the early and curable stages[11,14,29,31,37,46,47,66,89,103]. Since early carcinoma can exist in the normal-appearing cervix, the examining physician must decide whether to take a biopsy specimen, a vaginal smear, or both, in the routine examination of an ostensibly healthy patient[28,31,47,66]. If every physician's office is to serve as a cancer detection center, it follows that a thorough inspection of the cervix and a biopsy specimen of *every* cervical lesion should be taken[11,48], with a vaginal smear to supplement biopsy when possible[23,28]. Such an examination is generally accepted as minimal for patients in the suspected age group with *any* evidence of cervical disease; however, the diagnostic procedure for patients with no evidence of cervical disease is not so clearly defined[3,11,23].

Early carcinoma may appear as a slick, shiny spot which is a deeper red than the surrounding tissue[74]. Lesions which may simulate carcinoma are tuberculosis, syphilis, polyps, and cancer of the corpus or endocervical canal which appears at the orifice[58]. Polyps usually appear as soft, pedunculated masses of a deep, bluish-red color. Since some polyps may be cancerous

these require histologic examination[64]. In some instances, the cervix may appear grossly normal or may show only slight erosion[11,74]. Therefore, many lesions cannot be discovered without biopsy study[11] or examination of vaginal secretions. Even in cases of extensive carcinoma there is a variety of possible clinical findings and symptoms[47,104]. It is possible to find a histological Grade III carcinoma in a patient with minimal symptoms of short duration and with no significant gross alteration of the cervix on inspection or palpation[104]. Conversely, cases of early, slow-growing carcinoma with a long history of bleeding have been reported. The clinical findings and their interpretation will depend upon the experience of the examiner in many instances[5,85]. The Schiller iodine test is not specific for carcinoma but is valuable in determining whether a biopsy should be taken, as well as the site for the biopsy[3,51,66,74,103,108]. The test is made by applying Lugol's iodine solution with a swab to the surface of the cervix. The glycogen granules of normal cervical epithelial cells stain a deep brown, whereas diseased tissue does not stain. Light-staining areas usually signify cervical tears, granulomas, erosions, leukoplakia, or carcinoma[3]. Questionable lesions and lesions that may be confused with chronic cervicitis or with granulation tissue can be positively identified by biopsy[3,51].

Two major methods are used, currently, to diagnose early carcinoma of the cervix: the cervical biopsy and the Papanicolaou vaginal smear. The latter is being used with increasing efficiency to complement cervical biopsy in the diagnosis of early cancer. The smear is not, of course, intended to replace biopsy, but is valuable in supplementing biopsy findings[6,51,85]. For example, the report of a positive smear should certainly lead to intensive diagnostic study and biopsy, and a negative smear should not be construed as absolute evidence of the absence of cancer. Theoretically, the taking of a vaginal smear of every woman over 35 that is examined by any physician may seem ideal, but actually such a program is fantastically unrealistic. Vaginal smears are costly in terms of professional time, and trained cyto-pathologists that do such work throughout the country could not possibly examine more than a fraction of the material so collected[3]. Foote and Li estimate the incidence of cervical cancer in women over 35 years of age as one in 1500, so that if two slides were examined for each patient for a minimum of 10 minutes each, at least 500 hours of microscopic study would be required to reveal one carcinoma[28,109]. Such a program is possible for cancer detection clinics and other well-equipped outpatient clinics with sufficient laboratory facilities and personnel to carry out such examinations. Such clinics have explored and are continuing to explore the potentialities of the vaginal smear as a routine diagnostic measure. Miller, Riley and others have proved the silver staining method for vaginal and cervical smears to compare favorably in accuracy with the staining procedures of Papanicolaou and Traut[92]. An average of about 75 to 95% of cervical cancer can be detected by cytological study with only about 5% false negative results[92]. As a large-scale detection procedure, the use of routine vaginal smears affords certain advances over biopsy in the screening of thousands of patients in large medical centers[29]. From a practical and economic viewpoint, however, this routine procedure is beyond the scope of general practice. Therefore, in the physician's office, the vaginal smear can be used to supplement biopsy, but it should never be used to replace it, even if facilities

for cytological diagnosis are available.

Even with the diagnostic evidence of a positive vaginal smear, the final diagnosis must depend upon the microscopic examination of the cervical biopsy specimen[11,96] and treatment is never initiated without confirmation of the diagnosis by histological examination[85,108].

Several procedures have been developed to improve the fluid collection from within the genital tract to isolate exfoliated cells. One is the Marchetti cannula, a metal tube that can be inserted in the cervix to collect mucus or fragments of tissue[103]. The Murphy cervical spoon and the contraceptive diaphragm have also been used to collect material for smear studies[103]. Recently, a method utilizing the Draghi detection tampon has been advocated as a possible method of mass screening for the cytological detection of cervical cancer[86].

Valuable as exfoliative cytology is, however, there remains the need for confirmation by biopsy before treatment is begun[3,85,96]. Many methods of biopsy are used extensively. These include the Gusberg coning biopsy, Novak's spoon biopsy, the spatula scraping or "surface biopsy" of Ayre, the Newel-Budd biopsy knife, and the gelfoam biopsy of Gladstone[6,28,46,103,108]. There are advantages to all of these methods, although the simplest and most economical method is the four-quadrant biopsy taken from the cervical os[11]. The combination of vaginal and cervical smear with biopsy affords a high degree of diagnostic accuracy[46,51,85,92].

The colposcopy method of Hinselmann, and, more recently, colpomicroscopy are adjunctive methods of diagnosis[3]. Colposcopy has been used extensively abroad; however, it has not been used as much in this country because of the necessity of biopsy to confirm the visual findings[3,28,103]. A modification of the cytological approach has been introduced with the phase contrast microscope[3,64]. With this method, fresh vaginal secretions are examined in the physician's office. The disadvantage to this procedure is that a permanent record cannot be obtained except by photography or by a stained smear[3,64]. Another cytological method of examination of exfoliated cells is the Gusmano test, in which cells are crushed in order better to show the nuclear structure[3]. Investigation of the reduction of estrogenic activity accompanied by an elevation of betaglucuronidase in the vaginal fluid may provide the basis of a reliable test for invasive or preinvasive cancer of the cervix[32,59].

It is estimated that less than 50% of cervical cancers are discovered in the "early" stages, either Stage I or Stage II[28,104]. Therefore, there is a definite need for more extensive application of existing diagnostic tests[28]. Routine mass screening is not feasible except under special circumstances. Nevertheless, selective screening of patients with a high probability of cervical cancer is both practical and possible[28]. This selective screening must include frequent and meticulous examination with the vaginal speculum, and increasing use of cervical biopsy[58]. Formerly, surgical biopsy was done only in cases in which a gross cervical lesion was present. Obviously this practice has been insufficient in detecting early lesions[11], and adequate examination for the detection of cervical cancer must include cervical biopsy when there is any chronic lesion, absence of stain with Schiller's test, or an inconclusive vaginal smear[58,103]. The application of these diagnostic tests to more and more women, especially to multiparous patients in the susceptible age

groups, will result in increased detection of early cervical cancer[11,28].

Treatment. Several developments of recent years have altered the therapeutic approach to treatment of patients with cervical cancer. Among these is the increased frequency of early diagnosis so that eradication of localized lesions is more often possible[103]. Another major advance has been in the significant improvement of surgical techniques and their applicability to greater numbers of cancer patients[103]. Probably the most important development has been the evolution of individualized, precision dosimetry in radiation therapy[72].

It is generally agreed that radiation is the treatment of choice for nearly all cases of cervical cancer[4,42,50,56,62,63,65,75,78,87,98]. There are many conspicuous advantages to radiation therapy. For example, practically all cases can be treated with radiotherapy, while only a small percentage of patients are operable[65]. The risks are less and the mortality rate is about 1%[65]. Actually, there should be no mortality from irradiation[65]. In addition, while radiation results in atrophic changes, surgery means definite shortening of the vagina and alteration of function[18,65]. Finally, radiation therapy has resulted in the highest salvage and cure rates[14,55,63,65,98]. In general, there are five groups of patients for which radiation therapy is contraindicated[65]: patients who are radiation failures[30,50,98,106]; patients who cannot be given adequate therapy because of operative or anatomical defects[98]; patients with severe pelvic sepsis[30,38]; patients with other tumors or lesions which prevent adequate therapy[30]; and patients who refuse radiotherapy[18,65].

Carcinoma of the cervix, regardless of the histological type of the lesion, is responsive to radiotherapy[27]. Biologically, these lesions are also radiocurable, but radiocurability depends on the response of the tumor to radiation[106], and on the possibility of adequate irradiation of the entire tumor[26,27]. A major problem of treatment-planning is the choice of type of therapy which will afford the best likelihood of cure[50,75]. An obvious contraindication would be positive proof, early in the course of radiotherapy, of radioresistance of the tumor[19,40,62,98,106]. The frequency of radioresistance is low[63], although it has been estimated as high as 25% and, in smaller series, higher[87,104,106]. The clinical stage of the tumor is used as a guide in the selection of therapy[45,62], but radiation response cannot be predicted with accuracy on the appearance and clinical extent of the lesion[2,62]. Hence, it has been advocated that radioresistance can be estimated more accurately by study of vaginal smears or biopsy specimens before or during irradiation[19,41,42,55,62]. The method of determining the sensitization response is based on observation of changes in the normal basal cells in vaginal smears taken after test doses of irradiation[41,42,43,68].

Pronounced changes in the benign squamous epithelial cells are associated with an expected good response and minimal changes with poor response to radiation[41,43,68]. Although the test has proved a useful prognostic index in patients with cancer of the cervix, it has not been widely used because specialized training is required to evaluate the findings[19,43,45].

Most important, radiocurability depends upon adequate irradiation of the entire tumor with minimal damage to normal tissues[1,12,67,104]. Thirty years ago, a "smart dose of radium" was considered sufficient, and even this constituted a significant advance over the surgical results of that era[63,104,106]. At present, the greatest single advance in

radiotherapy is the establishment of the concept of tissue tumor dosage[4,67]. Radiation therapy is no longer empirically applied as an inflexible and preconceived treatment of so many roentgens in "air" or "skin" for every cancer patient[4,67]. Instead, an individualized system of dosage is used in which calculation of the radiation is made in tissue roentgens actually reaching the tumor[4,14]. Calculations based on the number of radium sources, location, strength, length, distance, and filter material provide data for conversion of milligram-hours of radiation into gamma roentgens[4]. This is, however, inadequate in determining the dosage that actually reaches the tumor; since the loss of intensity near the radium is high, there is variation in dosage throughout the tumor, and there is rapid decrease of radiation at points lateral to the intrauterine radium source[4]. Adequate dosage through the paracervical triangle and paravaginal tissue is necessary, because these are the major planes of extension of cervical cancer[33].

Of the many methods of clinical measurement of radiation, one of the most exact is that of preparation of isodose curves which show volume distribution of radiation for the individual patient[12,33], and in which calculations are made according to the size and shape of the tumor and anatomical variations[33,63,94]. Such complications as debility and infection must be taken into account and variations in the plan of treatment made accordingly[12,33,36,63,105]. With optimal placement of the radium source[94] it is possible to compute the tolerance levels for surrounding normal tissues. If, during treatment, direct readings in the bladder and rectum are made by means of a scintillation counter, the dosage can be kept safely below tolerance level[4,12,32,108]. This precaution reduces the danger of overdosage and prevents complications. Such a method requires special equipment and the services of a radio-physicist are necessary.

Other established methods of precision dosimetry utilize conversion factors for point and linear sources of radiation, from which it is possible to calculate tissue roentgens delivered to representative points within the pelvis[14]. Calculation of the radiation delivered to each tumor, to actual or potential metastases, and to surrounding normal tissues insures the greatest possible tolerance dosage for each patient. A survey of a 26-year period of treatment by different methods of radium application proves the need for precise dosimetry. In this study, correlation of measurements in the bladder and rectum, calculations of dosages delivered at different points, incidence of complications, and survival statistics revealed that the improved knowledge regarding distribution of intrauterine and vaginal ionizing sources has resulted in better survival rates and in decrease of complications[12,21].

An ideal homogenous distribution of radiation throughout the pelvis with radium alone is not possible[27,33]. In a recent study of 213 cases of squamous cell carcinoma, Stages I and II, metastases to the regional lymph nodes were found in 96 cases, or 45%, at operation after intracavitary radium treatment alone and without radiotherapy to the routes of dispersion of cervical cancer[19]. Intracavitary Curie-therapy implies irradiation of the pelvic midline with insufficient irradiation of the lateral aspects of the tumor because of the rapid fall in dosage gradient[4,9,21,40]; therefore, external irradiation is utilized to extend laterally the area of adequate dosage[27,33,60]. This combination of intracavitary radium and external roentgenotherapy has appreciably increased cure rates[25,39,62,63,65].

Precise determination of the tumor dose delivered by intracavitary radiation to the mid-line is necessary in order to integrate this dosage with that of external irradiation[14]. Also, several experimental approaches to therapy of the lateral pelvic lymphatics with radioactive isotopes have been reported[1,4,8,9,14]. With exact clinical dosimetry, the radiologist knows whether sufficient radiation can be delivered to the tumor and if patients should have surgery after radiotherapy[33,108]. For example, in cases in which the endometrial cavity has been invaded, it may be impossible to deliver a full tumor dose to the cervix, paracervical triangle, and the area of contiguous spread above the internal os into the uterine cavity. In such cases, total hysterectomy and lymph node dissection may be necessary to eradicate tumor tissue above the internal os[108]. Post-irradiation lymphadenectomy also has apparently increased survival rates in many cases[24,25,40,76,96]. Results have been further improved by the recognition and prompt treatment of complications which occur during therapy[33].

Some investigators are of the opinion that irradiation rarely destroys disease within the lymph nodes[68,75,76]. Recent reports, however, indicate that adequate primary irradiation is cancerocidal to diseased lymph nodes, at least in some cases[14,42,56,63,98]. Once a "curative" course of radiation has been given, irradiation of recurrent cancer may be contraindicated[63,106]. Irradiation of metastatic disease by various methods has not proved significantly successful[4], although roentgenotherapy has been useful as a palliative measure in nonoperable patients and patients not acceptable for routine radiotherapy[7].

Damages to normal tissues are more likely to occur in radium therapy than in roentgenotherapy[4]. The most serious injuries are those to the bowel and bladder[4,12,14,48,96]. In some cases, the symptoms that result from irradiation trauma may suggest a hopeless recurrence[27]. In many such instances, a pure necrosis without neoplasm may be found at necropsy[27]. Most radiation damage is not fatal, and complete recovery is possible in many instances if the patient is afforded exploratory operation, with blood transfusions, antibiotics, and other supportive measures[27,48,94]. Effective treatment for such complications often necessitates hospitalization[27,56]. So important is hospitalization for adequate therapy of complications of radiotherapy that one authority has stated that "hospitalization of all cases may in itself contribute considerably to improving the results"[27].

There is a major disadvantage in comparison of radiation and surgical treatment of cervical cancer patients, because surgery has been largely neglected during the past 25 years[4,50,104]. Intracavitary irradiation was adopted as almost the sole method of treatment immediately after the introduction of radium[63,104]. The abandonment of surgery was so apparent that in 1914 Wertheim remarked, "It is a tragic fate being obliged to establish the fact that my life's work, the introduction of radical surgery in the treatment of carcinoma of the uterine cervix, has been unprofitable"[63,104]. Thirty years after Wertheim, however, improvements in surgical techniques and in supportive measures[80] resulted in a complete reevaluation of surgical treatment in cancer of the cervix. Programs to assess the possibilities of radical surgery in cervical carcinoma were begun in different clinics throughout this country. Consequently, such investigative series of radical surgical treatment as are available are small when compared with the vast compilations of

statistics on radiation therapy[15,56]. From established results, surgery is recognized as the treatment of choice in certain highly selected cases, and its value remains controversial in others.

Since carcinoma *in situ* is a localized lesion and there is some evidence that it may be radioresistant[106], surgical excision is generally accepted as the treatment of choice[68,78,98,106]. As invasion may be present within a portion of the cervix not examined at biopsy, conservative measures are generally preservation of the ovaries without compromising the effect of complete removal of the lesion[98]. Radiation, of course, makes castration inevitable. In selected cases, Kottmeier[63] recommends careful observation of young patients during completion of childbearing before treatment is undertaken. Also, local removal of part or all of the cervix is performed by some surgeons in very young patients[63,74,96]. In general, however, a total abdominal hysterectomy is usually performed with preservation of the ovaries in premenopausal patients[98,103,106,108]. Some surgeons also prefer to excise the iliac and obturator nodes bilaterally[103]. Node excision may be of particular importance, since recurrences of tumors after total hysterectomy have been reported[44]. However, node dissection is unnecessary if the lesion is, by definition, limited to the cervix and invasive cancer is properly excluded by adequate biopsy before hysterectomy.

Surgery is also probably the treatment of choice in patients whose disease is proved radioresistant[30,42,62,87]. Once a full course of radiotherapy has been given, the tumor will not respond significantly to further irradiation[16,25,30,63,87,98,106], and there is risk of precipitating severe painful radionecrosis. According to Truelsen[104] about 35% of cervical carcinomas recur locally. Although in such cases significant salvage rate has not yet been achieved with radical surgery, individual successes are encouraging[105]. A number of patients with extensive, painful radiation necrosis may also be benefited by radical surgery[27,106]. In another group of patients, prolapse of the uterus precludes adequate irradiation[98]. In these patients surgery is preferred because of the difficulty of fixing the parametria during radiotherapy. Finally, the presence of multiple large fibroid tumors or ovarian cysts may interfere with complete irradiation, which in turn may result in pyometra[106]. In such selected instances, surgery may be the treatment of choice[105].

In efforts to improve the survival rates for patients with cervical cancer, innumerable surgical procedures and combinations of therapy have been proposed[25,40,72,77,80]. The many therapeutic methods may, for convenience, be considered according to their primary purpose, whether curative, prophylactic, or palliative.

In few clinics has radical surgery been advocated as the primary curative treatment. Although Meigs' famous series of 100 radical hysterectomies for invasive cancer has resulted in a 75% over-all 5-year cure rate with no operative mortality, this series represents only carefully selected patients[75]. In 1947, Brunschwig began a program in which all patients with cervical cancer were to be considered as surgical problems[15]. In actual practice, however, only 263 of 333 patients were considered operable, an operability rate of 79%[15]. Five types of surgery were employed, determined by the extent of the disease. Although in this series a "surgical" classification was used instead of the League of Nations classification, sufficient correlation is possible to allow statistical comparison. Of 218

patients in all classes in which surgery was performed, 48% were living and well, 4 to 5 years after surgery. About 35% of these were recurrent cases. Of 78 patients in Class A (microscopic evidence of disease confined to cervix), 80% were alive and well 4 to 5 years after operation. Of 53 Class E patients (direct invasion into bladder or rectum), 9, or 17%, had 4 to 5-year survival[15]. Although the surgical results in the early stages of cancer do not represent significant improvement over results obtainable with radiation, the improvement in the Class E cases affords considerable promise for radical surgery in far-advanced and recurrent disease[16]. One of the most frequent and serious complications of radical pelvic surgery is ureteral fistula. This complication is now being eliminated to a great extent by more precise surgical techniques that preserve the blood supply[75,76,80,106].

More frequent use of radical surgery has demonstrated that cancer cells are present in the lymph nodes much more often than was formerly realized[19,42,75,79,80,103]. Obviously, the extent and dispersion of cancer are important in the selection of therapy[49,103]; however, neither the clinical stage, the histologic appearance of the tumor, nor the gross appearance of the lymph nodes is sufficient for detection of cancer cells within the tissues[42,49]. For example, it has been shown that operative assessment of lymph nodes for tumor deposits by means of appearance and palpation is subject to error as great as 33%[19]. A method of demonstrating red fluorescence in lymphatic and cancer tissue with hematoporphyrin has been reported recently[90], and by this method detection of small or obscure cancer-bearing lymph nodes in cervical cancer surgery may be facilitated. This is a new development and has not been extensively investigated. Although the majority of patients with cancer of the uterine cervix die from effects of direct extension to contiguous organs, it is unusual to find evidence of lymph node involvement without evidence of contiguous spread[49]. For these reasons, various methods of "prophylactic" treatment have been devised to remove the routes of possible lymphatic spread and to remove the organs most likely to become sites of recurrence[40,49,97].

Many operations have been utilized to remove the routes of lymphatic spread and to prevent local recurrence[40,75,80,97]. There are many variations in surgical procedures because of individual preferences and also because of extent of local growth in the individual patient. The important result is that pelvic node excision has apparently increased the survival rates[15,40,68,75,77,79,80], especially when performed after complete radiation treatment, although this approach is mainly investigative at present, and only limited series have been reported. Dargent[24] reasons that preoperative radiation may sterilize microscopic foci of cancer cells in small lymphatics, whereas removal of metastatic deposits in lymph nodes is a surgical problem. He also emphasized that in certain cases of advanced but operable disease, there is no time for "radiation sterilization," since a delay of 6 to 8 weeks may afford time for extension of metastases to the great vessels of the lateral pelvic walls, which produces technical inoperability. Since lymph node metastases cause death in patients treated with either surgery or irradiation, combined therapy seems logical[24,25,72,79]. Schjott-Rivers has combined radiation and surgery for prevention of local recurrence and to remove, at as early a stage as possible tumors which are not radiosensitive, as well as possible lymphatic metastases[97]. In 116 cases, treated surgically after complete radium treat-

ment at the Norwegian Radium Hospital, 100 cases were followed for 5 or more years. There were 24 fatalities among the 100 patients. The author shows that operations for recurrence have given poor results and that prophylactic extirpation should therefore be considered justifiable as a possible preventive measure[97].

The effectiveness of radical surgery as a possibly curative measure for patients with far-advanced neoplasms has not yet been determined, although its value in palliation has been demonstrated in numerous selected cases[15,16,107]. Many radical surgical procedures have been employed in the elimination of severe complications in arrested cases or to restore organ function[14,48,98]. These surgical measures include a group of operations in which total hysterectomy and bilateral salpingo-oöphorectomy are combined with removal of various adjacent tissues and organs. The most radical procedure is total pelvic exenteration, in which the entire visceral contents of the pelvis, bladder, uterus, adnexae, vagina, rectum, lower ureters, pelvic nodes, and contiguous fatty tissues, are resected[15,16]. The ureters are implanted into the sigmoid and wet colostomy is established. The operation is performed when all viscera of the pelvis are actually or probably involved by cervical carcinoma. Extension of disease beyond the pelvis is a contraindication for partial or total pelvic exenteration[16]. It has been shown that removal of all or most of the pelvic viscera can be accomplished with comparatively low surgical mortality and morbidity[15,16,75,107]. For example, among 104 minimally selected patients with pelvic cancer subjected to exenteration, 12% survived 5 years[16]. These operations were performed only for palliation, since the patients had either recurrence or extensive disease. In cases of advanced disease in which radiotherapeutic relief is not possible, pelvic exenteration may represent the only hope of palliation. In some cases, the palliative results have lasted over a period of months or years[16,75], with physiological readjustment of the patient allowing comfortable, useful, and active life[75,107].

In patients with advanced cancer in which neither radiation nor surgery can be used, chemotherapeutic methods have been advocated. Diethylstilbestrol has been found an effective agent for hemostasis in incurable patients with profuse bleeding[73,81,82]. In some cases, epithelization of the lesion was produced[73] and sufficient palliation afforded to suggest to some of the patients that a cure had been effected[81,82]. Results of clinical trials of intra-arterial nitrogen mustard therapy suggest that this substance also may be useful in palliative treatment, either alone or as a possible adjunct to radiation therapy[8,22].

Results. The best method of evaluation of different therapeutic techniques is by comparison of survival rates. Complete evaluation of modern radical surgery in the treatment of cancer of the cervix is not yet possible. It is even difficult to compare results among various clinics because of differences in operative techniques and in criteria for selection of patients for surgery. It can be determined that results of surgery so far reported have not been as successful as those obtained by radiation. Surgical results may, however, attain a cure rate comparable with that of irradiation and, in selected instances, cure patients who would not otherwise be salvaged[75]. The statistics published in the latest volume of the *Annual Report on the Results of Treatment in Carcinoma of the Uterus* (Volume 9) show that in institutions that use primary surgery the 5-year recov-

ery rate in Stage I lesions is 62.5%, in Stage II, 42.7%, and in Stages I and II, 49.8%. In institutions with comparable series of patients where primary radiotherapy is used, the corresponding rates are 65.3%, 45.9%, and 51.8%[55]. In individual reports of results with radiation and surgical therapy combined there are indications that such combined therapy may afford increase in survival rates[24,25,72,79].

The ninth *Annual Report* includes statistics from 72 institutions in 17 countries. The reported figures furnish data on 87,424 patients, of which group 81,576 were treated by radiation. The statistics for patients treated from 1943 through 1947 show a relative recovery rate according to stage as follows: Stage I, 63.1%, Stage II, 44%, Stage III, 24.3%, and Stage IV, 8.3%[55]. The over-all recovery rate of all stages is 38.3%. In some institutions using radiation therapy, over-all recovery rates as high as 53.7% were reported[55]. No individual institution has comparable results in 5-year survival after radical surgical treatment.

Summary. In most cases of cervical cancer it is agreed that irradiation is the treatment of choice, since the proved cure rates thereby obtained are higher than from other forms of therapy. There is evidence, however, that post-radiation intra- and extra-peritoneal lymphadenectomy may improve the results. It is both specious and unrealistic to reason that most patients should receive radiation therapy because good radiotherapy is the more easily available. Actually, the "treatment of choice" should be individualized to such an extent that the best of radiation methods and the best of surgical procedures afford the best possible treatment for each patient. There is little question that appropriate surgery is indicated for recurrent cancer of the cervix after radiation failure. It has, however, been repeatedly emphasized that any attempt at surgical therapy which consists only of the "classical total hysterectomy" is to be deplored. Total hysterectomy without parametrial and pelvic lymph node excision will give results inferior to modern radiation therapy, as has been demonstrated during the past decades. It is evident from the literature that the full gravity of lymph node involvement, whatever type treatment is used, has not been wholly realized. The comparative efficacy of radical surgery in eradication of such involvement remains unknown. Whether current surgical results represent inadequate removal or whether properly performed radical surgery can destroy disease within the lymphatics remains to be determined.

Since it has been proved that specific amounts of radiation should be delivered to each predetermined volume of tumor tissue, precise clinical dosimetery is being steadily improved. Empirical methods of radiotherapy are no longer tenable if present cure rates are to be bettered. Actually, "cure rate" is an inaccurate term, since almost 10% of deaths occur from 5 to 10 years after therapy. It has been suggested that "survival rate" is the more appropriate expression of therapeutic results. Also, the question of how many true Stage III and Stage IV lesions are destroyed and how many of the "cures" represent error in assessment of the exact stage of the disease remains unanswered.

Finally, the solution to the over-all problem of carcinoma of the cervix seems to lie in earlier diagnosis. In many cases, recurrent and advanced disease can be and has been cured. It is the opinion of many investigators, however, that few of the really advanced cases can be cured by present methods. Since it is in the early

stages that the best therapeutic results are obtained, early diagnosis will, obviously, afford the best chance of cure.

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SUMMARIO IN INTERLINGUA

(See page 660 for original article)

Le Uso Clinic de Erythromycina

Un serie de 88 patientes con pneumonia causate per un varietate de organismos esseva tractate con doses de 400 mg erythromycina a intervallos de 6 horas. Le responsa esseva favorabile, non importa si le pneumonia esseva causate per pneumococcos, streptococcos, staphylococcos, o organismos mixte. Le resultatos clinic esseva de accordo con studios de sensibilitate executate in vitro.

Un sol caso mortal poteva esser considerate como debite a pneumonia in despecto de adequate therapia a erythromycina. Super le base del plus stricte criterios, 3 altere patientes habeva disfallimentos del therapia.

Un serie de 20 patientes con infectiones respiratori altere que pneumonia esseva tractate similemente. Iste serie includeva casos de pharyngitis, tonsillitis, otitis medie, bronchitis, bronchiectasis, e empyema. Omne iste casos monstrava un prompte melioration e recuperation, excepte le caso de un patiente con otitis medie causate per *Alkaligenes fecalis.*

Un serie de 14 patientes con infectiones miscellanee esseva tractate a bon successo con erythromycina. Iste serie includeva casos de furunculosis, blepharitis, osteomyelitis, abscesso subdiaphragmatic, septicemia e meningitis staphylococcal, erysipelas, e cellulitis.

Erythromycina monstrava un basse procentage de reactiones toxic. Un patiente disveloppava un eruption cutanee, un altere habeva febre que esseva possibilemente un reaction medicamentose. Un patiente se plangeva de nausea e vomito post erythromycina, e 4 patientes habeva diarrhea durante le therapia. Inter le total de 122 patientes recipiente 400 mg erythromycina a intervallos de 6 horas, il esseva necessari cessar le therapia a causa de effectos lateral in un caso.

Octo patientes con un historia de alcoholismo habeva delirio durante le curso del tractamento. Lor stato confuse esseva typic de lo que es incontrate in patientes con historias de alcoholismo durante sever attaccos de morbos acute.

BOOK REVIEWS AND NOTICES

UNTERSUCHUNG UND BEURTEILUNG DES HERZKRANKEN. By PROF. DR. H. W. KNIPPING, DOZ. DR. W. BOLT, DR. H. VALENTIN, and DR. H. VENRATH, Medical Department, University of Köln. Pp. 461; 265 ills. Stuttgart: Ferdinand Enke Verlag, 1955. Price, DM 79.

THIS is a highly scientific presentation and the more valuable since the practical problems in the management of the patient are stressed. It is the teamwork of a cardiopulmonary research group, well balanced in the integration of laboratory and clinical data.

All methods used are described in detail and many practical applications are stressed. Problems of anesthesia and of intra- and postoperative complications are discussed. Evaluation of cardiac and pulmonary function tests is given in great detail.

There is a large chapter on the diagnosis of congenital and acquired cardiac lesions with particular reference to problems of cardiac surgery. And special consideration is given to the cor pulmonale. The requirements for a cardiac laboratory are described, together with cardiac catheterization and angiocardiography; and the use of isotopes is discussed.

There are 60 pages of bibliography. This book is one of the best contributions to cardiography in recent times. H. R.

CANADIAN CANCER CONFERENCE, VOLUME 1. PROCEEDINGS OF THE FIRST CANADIAN CANCER RESEARCH CONFERENCE, HONEY HARBOUR, ONTARIO, JUNE 16–19, 1954. Edited by R. W. BEGG, Department of Medical Research, University of Western Ontario, London, Canada. Pp. 443; illustrated. New York: Academic Press, Inc., 1955. Price, $8.80.

THE cancer workers of Canada deserve considerable praise for holding such a Conference as described in about 400 pages of its Proceedings. The panorama explored in the various fields of this complicated question is remarkably well treated not only by Canadian workers, but also by invited American and European scholars. Five large subdivisions form the essence of the Conference. These consist of sections on:

(1) EXPERIMENTAL TUMORS. The biological background is surveyed by Andervont from the National Cancer Institute in Bethesda. The question of cultivation of tumor cells and the transplantation of neoplasms are considered. Steiner discusses his original views on the nature of neoplasm as the result of a parthenogenetic process in somatic cells subjected at first to some sort of cellular injury.

(2) TUMOR-HOST RELATIONS. This very interesting relation is taken up by a number of workers. Mider points out the possibility that the cancer cell has perhaps more ways of synthesizing its protoplasm than has the normal cell. The lipid metabolism in cancer with the marked decrease in neutral fats and fatty acids is pointed out. The relation of peptide to enzymatic reactions is discussed, besides various other biochemical problems in relation to growth.

(3) CANCER OF THE LUNG is taken up in an informal way. Hueper brings up the point that there are numerous environmental factors concerned in the development of cancer of the lung. A single factor has never been shown to be responsible for the development of lung cancer. To the reviewer it seems that possibly mild nonspecific cellular injury induced by various environmental factors may be the basic mechanism concerned in inducing such neoplasms in genetically susceptible individuals.

(4) ENZYMES and intermediary carbohydrate metabolism in an analysis of the pathways involved in the metabolism of tumor are considered at length. Quastel presents an interesting discussion of carbohydrate metabolism in cancer. Nucleic acid metabolism is likewise well treated in this Conference.

(5) IONIZING RADIATIONS. This important field of cancer research is considered thoroughly. Furth discusses in an interesting way his experiences during the last 25 years with ionizing radiation. He starts by confirming earlier clinical reports, with his studies on the induction of leukemia in 1928 in some stocks of mice. The appearance of ovarian and mammary tumors in female mice exposed to Roentgen-rays had also then been observed. The importance of inflammation in increasing the sensitivity of radiated cells to tumorous changes is pointed out. The rôle of the thymus in leukemia and the effect of radiation on that structure is considered.

The thyrotrophic pituitary tumors are discussed. This lecture contains an enormous amount of information which indicates that ionizing radiations can be mutagenic, carcinogenic, and carcinolytic. The reviewer wonders whether here again the *degree* of induced cellular injury with the consequent production of various chemical factors elaborated in turn in an inflamed area by injured cells (for example, necrosin, or the recently described proliferative factor) may not be important considerations in helping to understand the variations obtained by ionizing radiations.

The cancer researcher will find this Conference fruitful reading, for he will discover a definite and praiseworthy effort at integrating modern cancer research. V. M.

PROLONGED AND PERPLEXING FEVERS. By CHESTER S. KEEFER, M.D., Professor of Medicine, and SAMUEL E. LEARD, M.D., Instructor in Medicine, Boston University. Pp. 248. Boston: Little, Brown & Company, 1955. Price, $5.50.

THIS book is an interesting and valuable presentation of a subject that has baffled every clinician. The first section deals with both normal and certain probably abnormal but unexplained variations in body temperature (for example, periodic fever) and with diagnostic procedures. The second section deals with infectious fevers that may be prolonged and hard to recognize. Section 3 deals with noninfectious causes of fever such as tumor, blood dyscrasias and fevers in diseases that are neither infectious nor neoplastic, such as allergy, liver diseases, and others. There are numerous illustrative case reports as well as pertinent discussions drawn from over two hundred articles in the medical literature. Every physician will find in this volume much of practical value. R. K.

NEW BOOKS

Reserpine in the Treatment of Neuropsychiatric, Neurological, and Related Clinical Problems. By F. F. YONKMAN, F. L. MOHR, J. L. GRAEME, and others. Ann. New York Acad. Sci., **61**, 1, 1955. Pp. 280; illustrated. New York: New York Academy of Sciences, 1955. Price, $3.50.

A SYMPOSIUM of thirty papers by 58 authors on various aspects of reserpine in the treatment of neuropsychiatric, neurological and related clinical problems. R. K.

Die cervikalen Vertebral-Syndrome. By R. JANZEN, W. TÖNNIS, F. REISCHAUER, G. PARADE, W. KRENKEL, K. J., ZÜLCH, U., METZ, V. MORGENSTERN, W. WEBER, H. KUHLENDAHL, V. HENSELL, H. FELTEN, and L. ZUKSCHWERDT. Pp. 71; 5 ills. Stuttgart: Georg Thieme Verlag, 1955 (Intercontinental Medical Book Corporation, New York, U. S. Agents). Price, $1.85.

THE book represents the reports of a symposium dealing with the syndromes produced by discs of the cervical spine. The participants were surgeons, internists and neurologists of the Lower Rhineland and of Westphalia. The clinical neurological picture is outlined by Janzen and by Metz, its mechanism by Zulch, and by Kuhlendahl, the relationship to cardiac symptom by Parade, the neural origin of humeroscapular periarthritis by Morgenstern, the effect upon the spinal cord by Kuhlendahl, surgical treatment by Toennis and Krenkel, conservative treatment by Reischauer, chiropractic manipulations by Zukschwerdt, medico-legal problems by Weber. While the reports and the following discussion vividly demonstrate the complexity of the problems involved, the roentgenologic aspects are only occasionally mentioned and roentgenograms are entirely missing. E. S.

Schizophrener Prozess und Schizophrene Symptom-Gesetze. By DR. O. H. ARNOLD, Assistant, University Psychiatric-Neurologic Clinic, Vienna. Pp. 85; 16 ills. Vienna: Verlag für Medizinische Wissenschaften. 1955 (New York: Intercontinental Medical Book Corporation, U. S. Agents). Price, $3.75.

THIS book is based on a comprehensive study of schizophrenic patients studied in the University Psychiatric Clinic in Vienna. Starting with C. Schneider's functional analytic concept, the author attempts to develop a hypothesis concerning the prognostic import of various schizophrenic symptoms that may develop. An intensive statistical analysis of the various categories and frequencies of symptoms found, along with many comprehensive tables, make this a detailed and scholarly work. S. H.

NEW EDITIONS

Clinical Toxicology. By CLINTON H. THIENES, M.D., PH.D., Director, Institute of Medical Research, Collis P. and Howard Huntington Memorial Hospital, Pasadena, California, and THOMAS J. HALEY, PH.D., Associate Clinical Professor of Medicine, University of California at Los Angeles. 3rd ed. Pp. 457. Philadelphia: Lea & Febiger, 1955. Price, $6.50.

IN the present revision newer poisons and antidotes have been added. As in the previous

edition, the toxicology of the various agents is briefly discussed in the first half of the book. There is a section on principles of treatment and an outline of symptom diagnosis. The remaining 160 pages are devoted to descriptions of procedures for the identification and quantitative estimation of poisons in necropsy material. This volume is written as a classroom text and for the use of the general practitioner. The medical student and practitioner may prefer a textbook in which the signs and symptoms and treatment of poisoning are more fully described. The brevity of this volume sometimes results in misleading statements. For example, along with more desirable agents, strychnine is mentioned as an agent for combating low blood pressure, and lobeline, camphor and sodium cyanide as stimulants for use in respiratory failure. D. C.

Clinical Biochemistry. By Abraham Cantarow, M.D., Professor of Biochemistry, Jefferson Medical College, and Max Trumper, Ph.D. 5th ed. Pp. 738; 54 ills. Philadelphia: W. B. Saunders Co., 1955. Price, $9.00.

The profession will welcome the new edition of this standard text, thoroughly revised and brought up-to-date. R. K.

An Historical Chronology of Tuberculosis. By Richard M. Burke, M.D., Assistant Professor of Medicine, University of Oklahoma School of Medicine. 2nd ed. Pp. 125; 6 ills. Springfield, Ill.: Charles C Thomas, 1955. Price, $3.75.

In this small volume the author lists about 500 discoveries and events which pertain directly to the history of tuberculosis. The material is divided into three periods: the Ancient Period (5000 B.C. to 1600 A.D.); the Pre-Modern Period (1600 to 1800); and the Modern Period which is subdivided into two parts, 1800 to 1881, and 1882 to the present. There is a valuable general bibliography of some 476 references.

Physicians interested in the historical development of our knowledge of tuberculosis will find this book particularly useful. C. Z.

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The Effects of Reserpine and Chlorpromazine on Gastric Secretion. By BERNARD J. HAVERBACK, M.D., THOMAS D. STEVENSON, M.D., ALBERT SJOERDSMA, PH.D., M.D., and LUTHER L. TERRY, M.D. 601

The Interacting Effects of Public Health, Fertility Behavior and General Economy on Standards of Living. III. Quantitative Evaluation of Component Determinants with Respect to Raising or Maintaining Present Standards. By ALEXANDER LANGER, M.D., and PAUL S. HENSHAW, PH.D. 605

The Rectal Absorption of Mercaptomerin Labeled with HG^{203}. By JERRY K. AIKAWA, M.D., and WILLIAM R. CARLSON, M.D. 622

The Relationship of Cirrhosis of the Liver to Hypertension: A Study of 504 Cases of Cirrhosis of the Liver. By HUBERT F. LOYKE, M.D. 627

A Simple Micromethod for Determination of Bilirubin in Plasma. By JAMES H. GRAHAM, M.D. 633

The Effect of Sitosterol Administration upon the Serum Cholesterol Level and Lipoprotein Pattern. By CLAUDE JOYNER, JR., M.D., and PETER T. KUO, M.D. 636

Simultaneous Determination of Cardiovascular-Renal Functions in Man by a Constant Infusion Technique. By CHARLES H. HENDRICKS, M.D., EDWARD J. QUILLIGAN, M.D., LEO A. SAPIRSTEIN, PH.D., M.D., ANDREW J. PULTZ, A.B., M.S., and MORRIS J. MANDEL, A.B., M.S. 648

Local Cutaneous Response of Nicotinic Acid and Esters as Diagnostic Aid for Rheumatoid Arthritis. By PAUL LEIFER, M.D., and ROBERT C. BATTERMAN, M.D. 657

The Clinical Use of Erythromycin. By SAUL SOLOMON, M.D., and BARBARA JOHNSTON, M.D. 660

Progress of Medical Science

Pediatrics—A Review of Porphyrin Metabolism with Special Reference to Childhood. By ROBERT A. ALDRICH, M.D., ROBERT F. LABBE, PH.D., and ELLEN L. TALMAN, PH.D. 675

Gynecology and Obstetrics—A Five-Year Survey of the Literature in Cancer of the Cervix. By JOHN A. WALL, M.D., F.A.C.S. 698

Book Reviews and Notices 714

Complete contents on adv. page 8

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CONTENTS

ORIGINAL ARTICLES

The Effects of Reserpine and Chlorpromazine on Gastric Secretion 601
By BERNARD J. HAVERBACK, M.D., THOMAS D. STEVENSON, M.D., ALBERT SJOERDSMA, PH.D., M.D., and LUTHER L. TERRY, M.D., Bethesda, Maryland.

The Interacting Effects of Public Health, Fertility Behavior and General Economy on Standards of Living. III. Quantitative Evaluation of Component Determinants with Respect to Raising or Maintaining Present Standards 605
By ALEXANDER LANGER, M.D., and PAUL S. HENSHAW, PH.D., New York, New York.

The Rectal Absorption of Mercaptomerin Labeled with HG^{203} 622
By JERRY K. AIKAWA, M.D., and WILLIAM R. CARLSON, M.D., Denver, Colorado.

The Relationship of Cirrhosis of the Liver to Hypertension: A Study of 504 Cases of Cirrhosis of the Liver 627
By HUBERT F. LOYKE, M.D., Cleveland, Ohio.

(Contents continued on page 10)

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A Simple Micromethod for Determination of Bilirubin in Plasma 633
By JAMES H. GRAHAM, M.D., Boston, Massachusetts.

The Effect of Sitosterol Administration upon the Serum Cholesterol Level and Lipoprotein Pattern 636
By CLAUDE JOYNER, JR., M.D., and PETER T. KUO, M.D., Philadelphia, Pennsylvania.

Simultaneous Determination of Cardiovascular-Renal Functions in Man by a Constant Infusion Technique 648
By CHARLES H. HENDRICKS, M.D., EDWARD J. QUILLIGAN, M.D., LEO A. SAPIRSTEIN, PH.D., M.D., ANDREW J. PULTZ, A.B., M.S., and MORRIS J. MANDEL, A.B., M.S., Columbus, Ohio.

Local Cutaneous Response of Nicotinic Acid and Esters as Diagnostic Aid for Rheumatoid Arthritis 657
By PAUL LEIFER, M.D., and ROBERT C. BATTERMAN, M.D., New York, New York.

The Clinical Use of Erythromycin 660
By SAUL SOLOMON, M.D., and BARBARA JOHNSTON, M.D., New York, New York.

(Contents continued on page 12)

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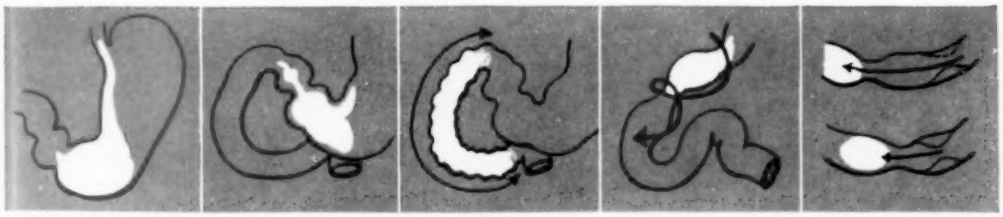

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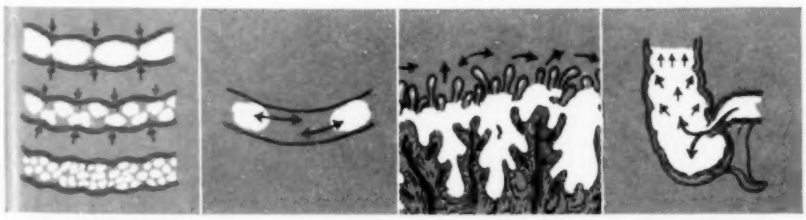

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(Contents continued on page 14)

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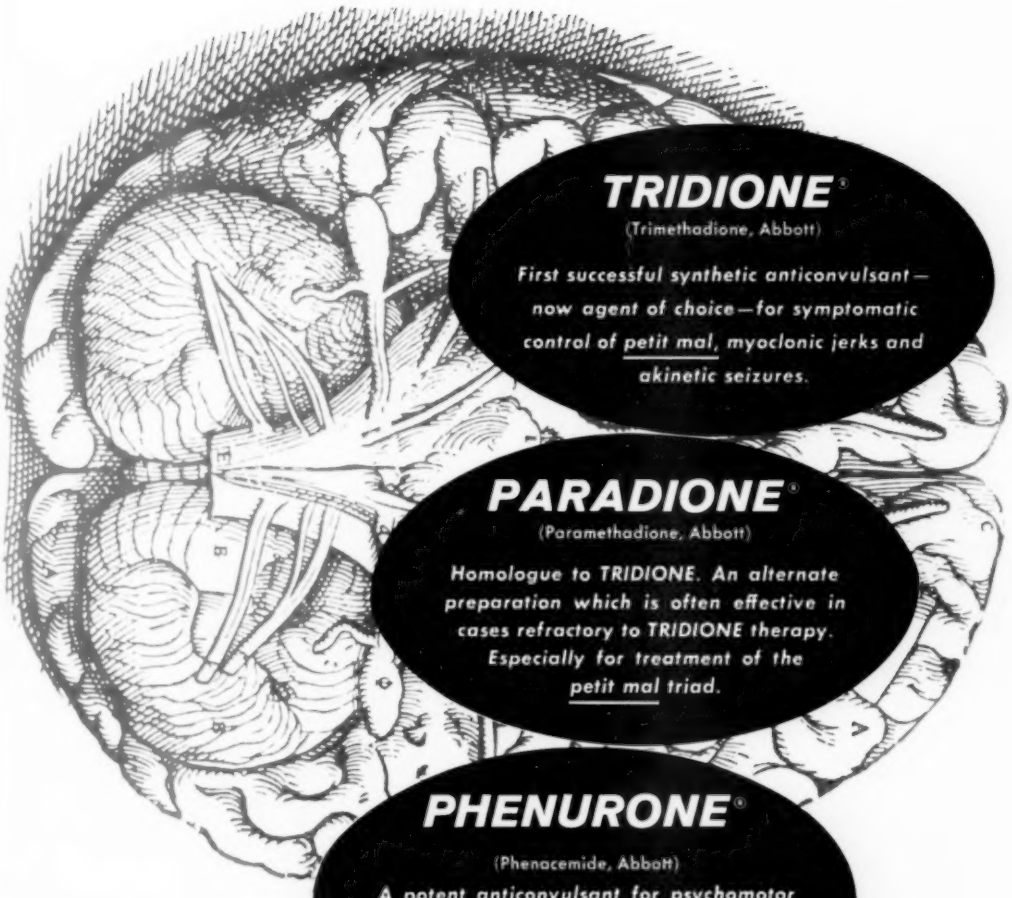

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CONTENTS—*(Continued)*

PEDIATRICS

A Review of Porphyrin Metabolism with Special Reference to Childhood 675
By Robert A. Aldrich, M.D., Robert F. Labbe, Ph.D., and Ellen L. Talman, Ph.D., Portland, Oregon.

GYNECOLOGY AND OBSTETRICS

A Five-Year Survey of the Literature in Cancer of the Cervix 698
By John A. Wall, M.D., F.A.C.S., Houston, Texas.

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(1) Payne, R. W.; Shetlar, M. R.; Farr, C. H.; Hellbaum, A. A., and Ishmael, W. K.: J. Lab. & Clin. Med. 45:331, 1955. (2) Bunim, J. J.; Williams, R. R., and Black, R. L.: J. Chron. Dis. 1:168, 1955. (3) Holbrook, W. P.: M. Clin. North America 39:405, 1955.

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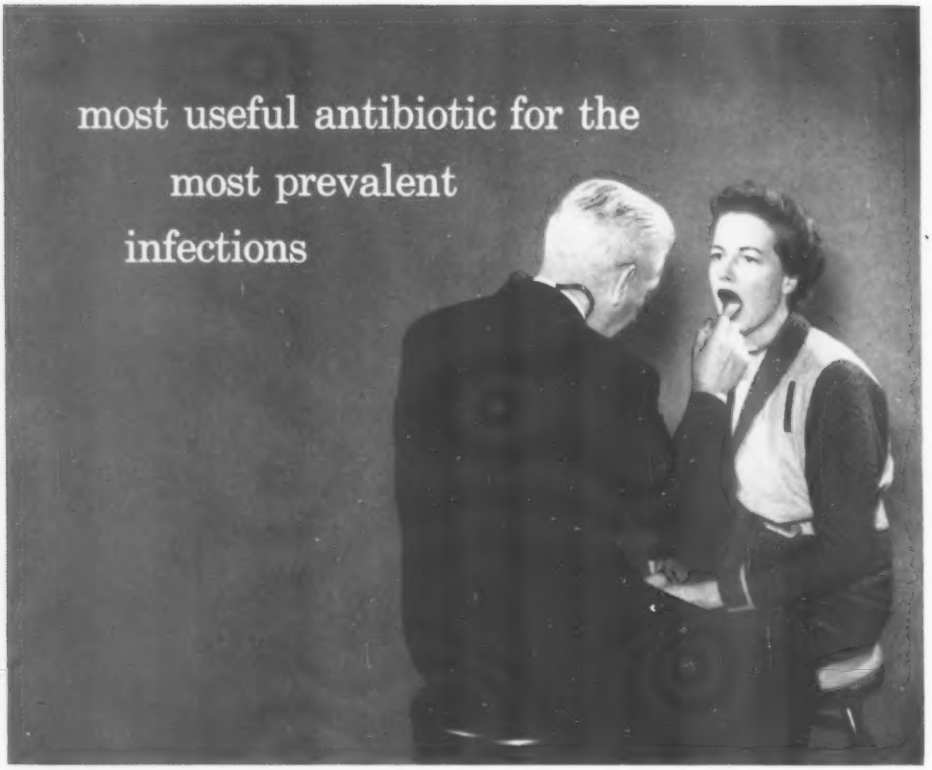

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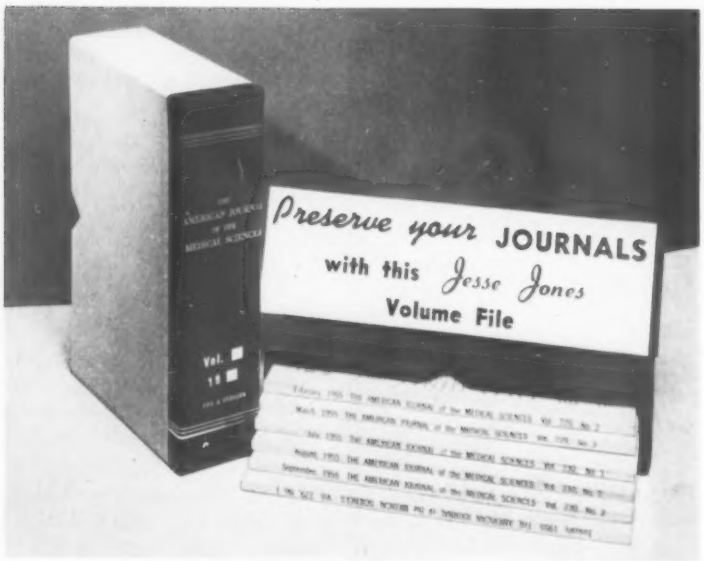

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Ayerst Laboratories 26
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Warner-Chilcott Laboratories ..... 3rd Cover
White Laboratories, Inc. 18
Winthrop Laboratories, Inc. ..... 4th Cover
Wyeth Incorporated 2, 7, 14

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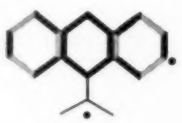

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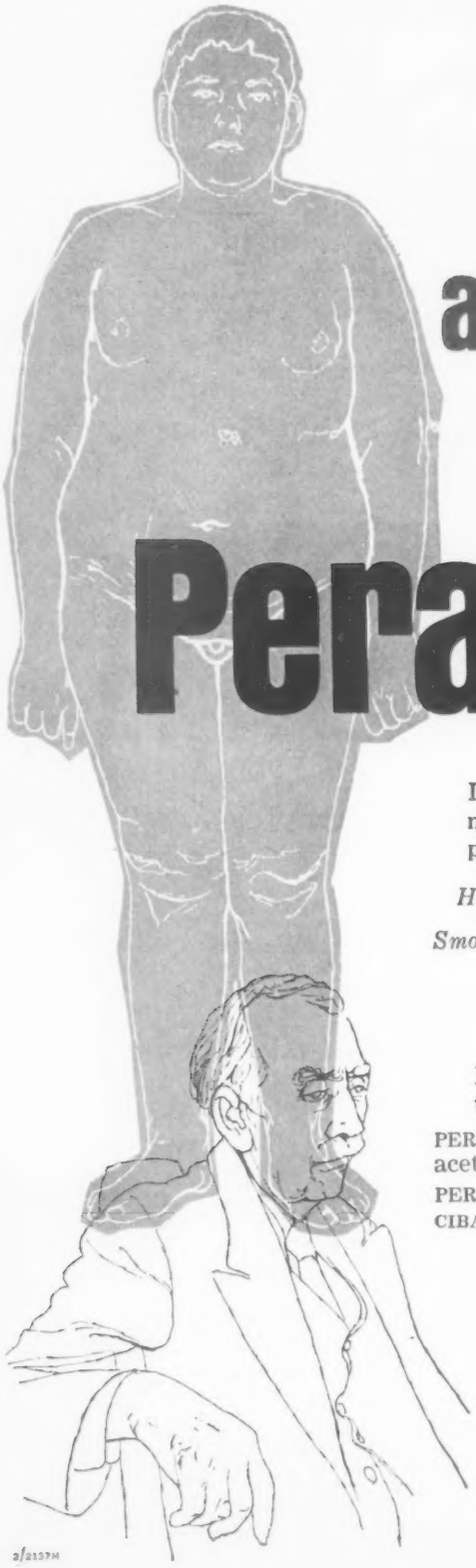

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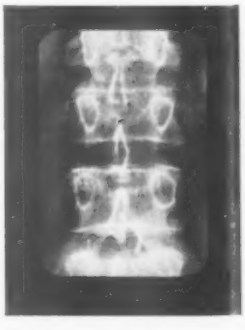

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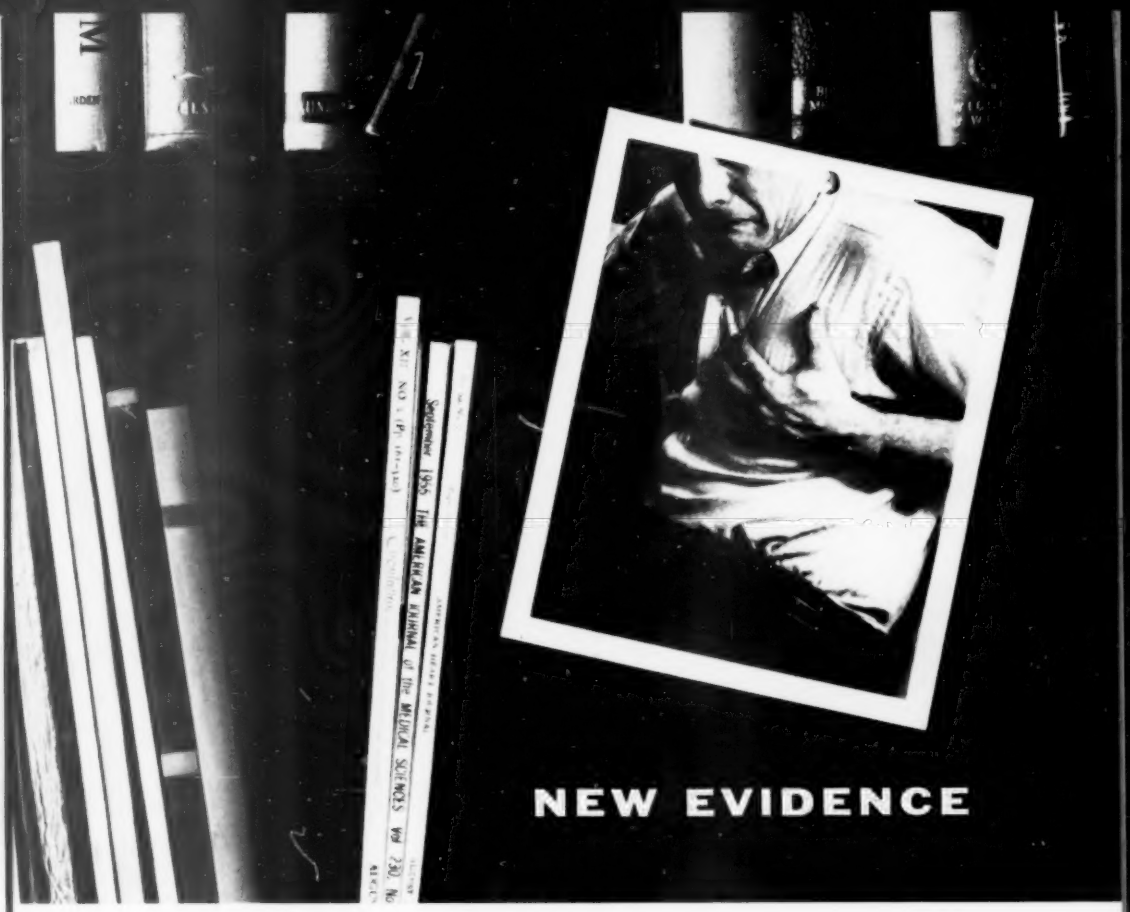

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